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New Chemistry of Imidazolinium ylides

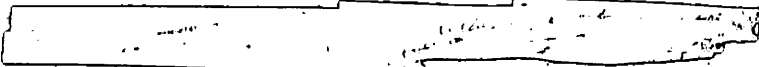
By

Pedro M. J. Lory

Thesis submitted to the Open University

For the Degree of Doctor of Philosophy

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To my parents

Declaration

I declare that the work presented in this thesis is the result of my own investigations, and where the work of others is cited, it is fully acknowledged. The material embodied in the thesis has not been submitted, nor is currently being submitted for any other degree.

Acknowledgements

I would initially like to thank Ray for his supervision and guidance throughout the 3 years. Secondly, many thanks go to a certain “intimidating” Geordie going by the name of Jim Iley whose help, friendship, supervision and stress-relieving Friday doughnuts largely contributed to the success of this project. Many thanks to Adrian Dobbs for the ever useful suggestions, advice and Thursday evening beers. A very warm thanks to my good mate Didier whose friendship and infectious motivation helped me through a lot of bad times throughout the past 3 years. Of course, none of this work would have been possible without the assistance of all OU staff, particularly, Pravin Patel, Jim Gibbs, Alan Leslie, Gordon Howell and Brandon Cook-so, many thanks to them. Thanks to all of those students in the group who made my life during these last 3 years a bit more enjoyable and sometimes easier, in particular “Auntie” Janet. Warm thanks to Sasa Martinovic for her friendship, tea and sympathy, to Fred, Austin and Isabel for having been such relaxed and easy-going house-mates and to Julie for having put up with me. Thanks, too, to the EPSRC MS Service (University of Wales, Swansea) and Crystallographic Service (University of Southampton). Finally, the biggest thanks of all go to my beloved parents without whose incredible friendship, love, patience and financial sacrifice, none of this would have been possible. *Muito obrigado a ambos. Nunca esquecerei o vosso esforco ao longo de todos estes anos...*

Abstract

Previous work in this group has shown 4,5-dihydroimidazolium ylides, formed by N-alkylation of 4,5-dihydroimidazoles, to undergo 1,3-dipolar cycloadditions with a range of dipolarophiles in a highly regio- and stereoselective fashion.

We have investigated two further aspects of this chemistry: (1) the synthesis of 4,5-dihydroimidazoles substituted with a heteroatom at C-2 and the subsequent N-alkylation of those templates followed by deprotonation to potentially access novel azomethine ylides; and (2) an intramolecular variant of the 1,3-dipolar cycloaddition, synthesising for this purpose a series of bromomethyl(ω -1)-oxoalkenoates as dipolarophiles and subsequently reacting these with some 4,5-dihydroimidazole templates.

The synthesis of 4,5-dihydroimidazoles substituted with a heteroatom at C-2 was developed from 1-benzyltetrahydroimidazol-2-thione **131**. Methylation of this with either iodomethane or methyl trifluoromethanesulfonate provided a key methylthioimidazolium iodide intermediate **135** from which 2-alkanethio- (**136**), 2-alkoxy (**137**) and 2-dialkylamino- (**138**) 4,5-dihydroimidazoles could be prepared by deprotonation, reaction with an alkoxide or reaction with a dialkylamine, respectively. N-Alkylation of the heterocycles was found to be unsuccessful. An alternative strategy, involving the synthesis of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one **143a** and -2-thione **143b**, was developed. The oxygen-containing compound **143a** was transformed into its corresponding *O*-substituted salts by treatment with triethyloxonium tetrafluoroborate, trimethylsilyl trifluoromethanesulfonate or trifluoromethanesulfonic anhydride. The sulfur analogue **143b** was *S*-methylated using methyl trifluoromethanesulfonate. However,

neither of the salts was found to undergo a 1,3-dipolar cycloaddition reaction upon treatment with DBU followed by methyl acrylate.

Intramolecular 1,3-dipolar cycloaddition reactions of a variety of α -bromoketones with 1-benzyl-4,5-dihydroimidazoles proved successful. Thus, reaction of 1-benzyl-4,5-dihydroimidazole **29** with methyl *E*-8-bromo-7-oxooct-2-enoate **196a**, followed by treatment with DBU afforded the tricyclic pyrroloquinoxaline adducts methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **217**. This arises from the primary cycloadduct undergoing a cascade involving an eliminative ring-opening, recyclisation, loss of water and prototropic shift cascade. Seven other examples of this reaction, involving 2- and 4-phenyl-4,5-dihydroimidazoles, and ethyl and *tert*-butyl *E*-8-bromo-7-oxooct-2-enoates are reported. However, the reaction fails with the corresponding *E*-10-bromo-9-oxodec-2-enoate, as well as with 2- and 3-methyl substituted octenoates (*i.e.* trisubstituted double bonds). In these cases no cycloaddition reaction involving the double bond occurs. In one instance, the reaction of (*R*)-4-phenyl-4,5-dihydroimidazole **112** with *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate **278**, we were able to isolate the primary cycloadduct, *tert*-butyl (3*R*,4*aR*,8*aS*,9*S*,9*aR*)-1-benzyl-5-oxo-3-phenyldecahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate **283**. It would appear that the combination of sterically demanding phenyl and *tert*-butyl groups precludes eliminative ring-opening.

Abbreviations

The following symbols and abbreviations are used in this text:

$[\alpha]_{\text{D}}^{20}$	specific rotation (measured with sodium D line, sample at 20°C), in $\text{degmol}^{-1}\text{cm}^{-2}$
aq.	aqueous
b.p.	boiling point
c	concentration (mol/dm^3)
cat.	catalytic
Cbz	benzyloxycarbonyl
COSY	two-dimensional correlated spectroscopy
CsF	caesium fluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
1,3-DC	1,3-dipolar cycloaddition
DCM	dichloromethane
<i>de</i>	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
Diglyme	<i>bis</i> (2-methoxyethyl) ether
DMSO	dimethylsulfoxide
<i>E</i> -	'entgegen'
equiv.	molar equivalents
Et	ethyl
FAB	fast atom bombardment

FMO	frontier molecular orbital
h	hours
HOMO	highest occupied molecular orbital
Hz	Hertz
IR	infrared
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
$M^{\bullet+}$	molecular ion peak
MH^+	protonated molecular ion isotopic peak
MNH_4^+	molecular ion peak determined by ammonia chemical ionisation mass spectrometry
MHz	megahertz
min	minutes
mmol	millimoles
m.p.	melting point
m/z	mass to charge ratio
NaH	sodium hydride
n-BuLi	n-butyllithium
NBS	N-bromosuccinimide
NBzl	nitrobenzyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate

RT	room temperature
<i>sec</i> -BuLi	<i>sec</i> -butyllithium
TBDMSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
<i>tert</i> -BuLi	<i>tert</i> -butyllithium
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane or trimethylsilyl
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
v/v	proportions of two components expressed as a ratio of their volumes
Z-	'zusammen'

Contents

1.0 Introduction	page
1.1 General introduction	1-5
1.2 The 1,3-dipolar cycloaddition reaction	5-6
1.2.1 The 1,3-dipole	6-9
1.2.2 The dipolarophile	9-10
1.2.3 Mechanistic issues	10-12
1.2.4 Stereochemistry	12-15
1.2.5 Regiochemistry	15-18
1.3 Azomethine ylides as 1,3-dipoles	19
1.3.1 Generation of azomethine ylides	20-25
1.3.2 Generation of chiral azomethine ylides	25-28
1.3.3 1,3-Dipolar cycloadditions of azomethine ylides	29-37
1.3.4 Chiral induction by the 1,3-dipole	37-41
1.3.5 Chiral induction by the dipolarophile	41-43
1.3.6 Chiral catalysis of 1,3-dipolar cycloaddition reactions	43-45
 2.0 Results and discussion	 46
2.1 Intermolecular approach	47
2.1.3 C-2 Substituted dihydroimidazoles and imidazolinium ylides in 1,3-dipolar cycloaddition reactions	 47-51

2.1.2 Strategy	51-53
2.1.3 Synthesis of dihydroimidazoles substituted at C-2 with heteroatoms and attempted 1,3-dipolar cycloaddition reactions.	53-89
2.2 Intramolecular approach	90
2.2.1 Strategy	90-93
2.2.2 Synthesis of α -haloketone dipolarophiles and their 1,3-dipolar cycloaddition reactions	93-137
2.3 Summary	138-139
2.4 Future work	140-142
3.0 Experimental	143
3.1 Intermolecular approach experimental	145-179
3.2 Intramolecular approach experimental	181-222
References	223-233
Addendum	234-238
Appendix: X-ray crystallographic data	239-243

Chapter 1

Introduction

1.1 General Introduction

Of the vast array of structures which organic compounds adopt, many contain ring systems as a component. When the ring is made up of carbon and at least one other element, the compound can be classified as heterocyclic. Many nitrogen-containing heterocyclic compounds occur naturally and their functions are often of fundamental importance to living systems: it is striking how often a nitrogen-heterocyclic compound is found as a key component in biological processes. We can, for example, identify the nucleic acid bases, which are derivatives of the pyrimidine (Figure 1) and purine (Figure 2) ring systems, as being crucial to the mechanism of replication. Others, such as levamisole (Figure 3), have found their use as potential anti-cancer agents.¹

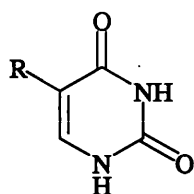


Figure 1

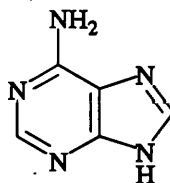


Figure 2

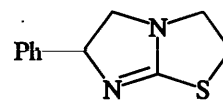
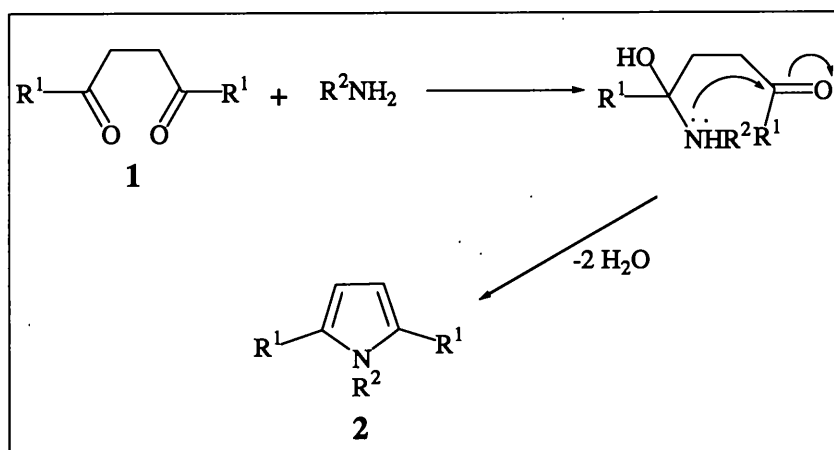


Figure 3

Many modern pharmaceuticals are totally synthetic compounds and a large proportion of these are heterocyclic. In other areas in which organic compounds are widely used, such as the pesticides and dyestuffs industries, heterocyclic compounds are also predominant. In laboratory synthesis, heterocyclic compounds are frequently a source of latent functionality.² The ring systems can be carried through many stages of a synthetic

sequence and then cleaved to produce delicate functional groups, often in a highly selective manner.

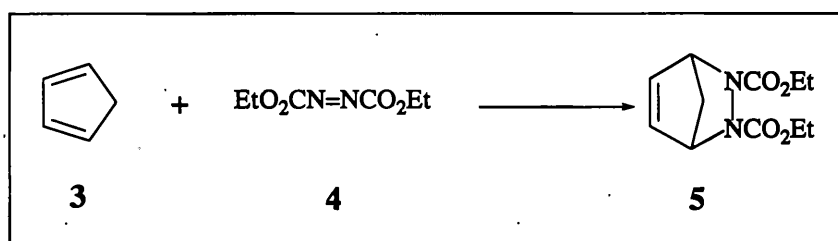
For many of the common heterocyclic ring systems there is a wide range of practicable synthetic routes available. These can vary in complexity from one-step syntheses using a single reaction component, to multicomponent procedures with a large number of steps. Heterocyclic ring-forming reactions are recognised as being in general the most useful synthetic tools towards the synthesis of nitrogen-heterocyclic rings.³ Cyclization reactions involving the formation of one bond in the ring-forming step, illustrated by the well known Paal-Knorr synthesis of pyrroles **2** from 1,4-dicarbonyl compounds **1** (Scheme 1) are amongst some of the most widely used approaches towards the synthesis of nitrogen-heterocyclic ring systems.



Scheme 1

The cyclization step is a nucleophilic attack on the carbonyl group, probably involving an intermediate species such as that shown in Scheme 1. The 1,4-diketone acts as an electrophile in both the initial step of the reaction of the amine and in the cyclization step. Many other heterocyclic syntheses of the cyclization type are analogous, in that an initial

electrophile-nucleophile interaction between two reagents is followed by a second such interaction in the cyclization step. In contrast, cycloaddition reactions⁴ are those in which two bonds of the new ring are formed in the cyclization step. These can provide routes to nitrogen-heterocycles with well-defined substitution patterns, and in many cases, with great stereochemical control. Undoubtedly, the synthetically most important types of cycloadditions are the Diels-Alder and the 1,3-dipolar cycloaddition (1,3-DC) reactions. The former reaction, discovered nearly half a century ago, is the prototypical thermal cycloaddition. Because six-membered rings are generated with remarkable stereoselectivity and regioselectivity, the reaction is of great synthetic utility. In addition, heteroatoms can be incorporated into the skeleton of the nucleophilic diene (electron-rich component) or of the electrophilic dienophile (electron-deficient component) to provide important routes to several six-membered heterocycles. For example, the Diels-Alder reaction of cyclopentadiene **3** with diethyl azodicarboxylate **4** to afford the pyridazine **5** is just one of the many synthetic examples (Scheme 2).



Scheme 2

The 1,3-DC reaction provides an excellent method for the construction of five-membered rings because a wide variety of 1,3-dipoles (a three-atom component) are available which can undergo addition to multiply-bonded systems that are defined as dipolarophiles (the

two-atom component).⁵ Its utility is such that it has acquired a prominent place in synthetic strategy for a variety of targets, including natural products such as sugars and alkaloids.^{6,7} Since our project has focused on the use of the 1,3-DC reaction, we shall discuss it in more detail.

1.2 The 1,3-dipolar cycloaddition reaction

The work of Huisgen and co-workers⁸ in the early 1960s led to the general concept of the 1,3-DC reaction and over the years this reaction has been widely explored in syntheses since many of the 1,3-dipolar species are readily available (or easily formed *in situ*) and are able to react with a wide variety of dipolarophiles.

1,3-Dipolar cycloadditions are bimolecular and involve the addition of a three-atom 1,3-dipolar component (a^-b^+c) to a two-atom multiply-bonded system ($d=e$ or $d\equiv e$), the dipolarophile, leading to five-membered heterocycles (Figure 4).

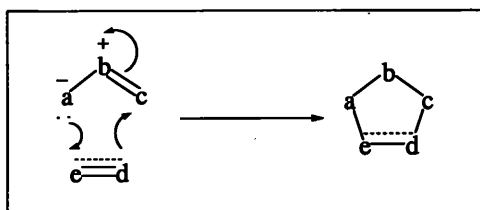


Figure 4: 1,3-Dipolar cycloaddition

The versatility of 1,3-dipolar cycloadditions arises from: (1) the wide array of available dipoles and dipolarophiles; (2) the concerted, that is stereoconservative, mechanism of the cycloaddition; (3) the latent functionalities within most cycloadducts, which can allow for

subsequent transformations, including ring-opening. The ever-increasing volume of 1,3-DC literature testifies to its growing importance and use in modern synthetic chemistry.^{9,10,11}

1.2.1 The 1,3-dipole

The first molecule to act as a 1,3-dipole, diazoacetic ester, was discovered some 70 years ago by Curtius.¹² However, general application of 1,3-dipoles in organic chemistry was established by the systematic studies of Huisgen and co-workers in the 1960s.¹³ Since then, a variety of dipolarophiles have been discovered¹⁴ but only a few dipoles have found general application in synthesis.

The 1,3-dipole is a 3-atom species represented by ground state zwitterionic resonance structures, one of which has the formal charges at the termini (Figure 5a).

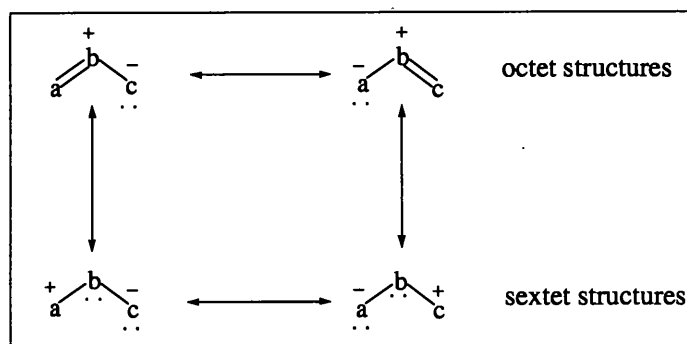


Figure 5a: Resonance structures of allyl anion-type 1,3-dipoles

A feature shared by all 1,3-dipoles is an allyl anion-type π -system, *i.e.* four electrons in three parallel atomic p-orbitals. In contrast to the allyl anion, where the middle atom has no

formal charge, 1,3-dipoles feature an “onium” centre *b* (Figure 5a). In addition, two of the four allylic π -electrons of the 1,3-dipole can be envisaged localised at the central atom *b*, therefore cancelling the onium charge. As a consequence, resonance structures can be drawn in which electron sextets are created at atoms *a* or *c*. Whereas the terminal centres of the allyl anion are always nucleophilic, those of 1,3-dipoles have both nucleophilic and electrophilic character. This ambivalence is shown by the sextet canonical forms (Figure 5a) and this is essential towards understanding the reactivity in these systems.

A second, and smaller, class of 1,3-dipoles is the propargyl/allenyl-type which arise from the incorporation of an additional π -bond in the 1,3-dipole system in the plane perpendicular to the allyl anion molecular orbital (MO) (Figure 5b). One of its resonance forms will thus contain a triple bond and dipoles of this type are linear (Figure 5b) in contrast to the bent allyl anion-type 1,3-dipoles (Figure 5b). Occasionally, the two classes of 1,3-dipole described thus far, are drawn as hypervalent resonance forms (Figure 5c), but these require the central atom to possess appropriate atomic orbitals to accommodate the additional electron density at that atom that these structures imply.

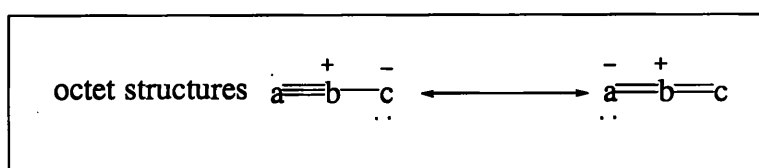


Figure 5b: Propargyl/allenyl-type 1,3-dipoles.

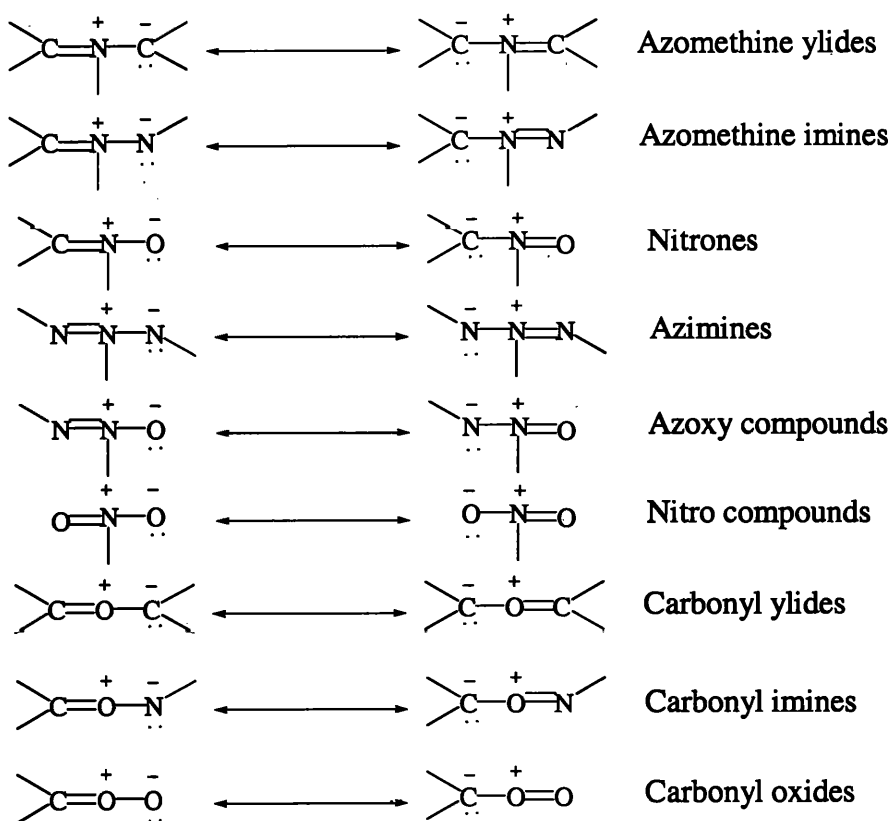


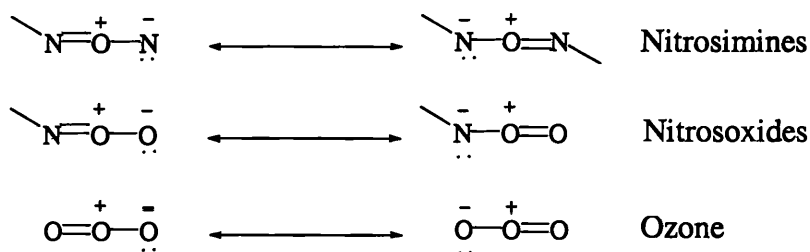
Figure 5c: Hypervalent representations.

Restricting the permutation of the three atoms of the 1,3-dipole to the second period elements C, N and O, and bearing in mind that for atom *b* in 1,3-dipoles of the propargyl/allenyl-type the choice is limited to an atom of the group XV elements (since only the latter can bear a positive charge on its tetravalent state), Huisgen proposed six 1,3-dipoles of the propargyl/allenyl-type and twelve of the allyl-type (Table 1).¹⁵

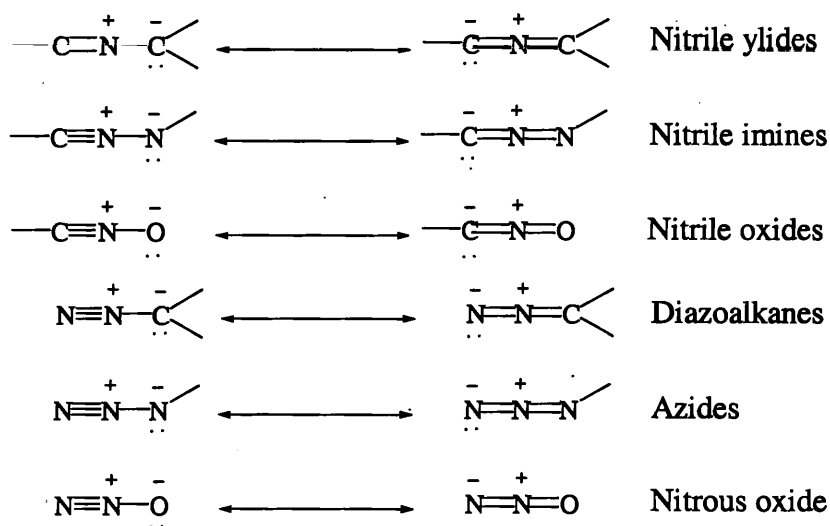
Table 1: Classification of heteroatom 1,3-dipoles

Allyl-type 1,3-dipoles





Propargyl/allenyl-type 1,3-dipoles



1.2.2 The dipolarophile

It is easy to envisage a vast number of multiply-bonded compounds which can act as dipolarophiles but by far the most useful and commonly employed are alkenes. Other dipolarophiles widely used are alkynes ($\text{RO}_2\text{C}\equiv\text{CO}_2\text{R}$), isocyanates (RNCO), conjugated carbonyls ($\text{CH}_2=\text{C}(\text{H})\text{COR}$) and thiocarbonyls ($\text{CH}_2=\text{C}(\text{H})\text{CSR}$).

The nature of the dipolarophile (functionality, reactivity, shape, size and propensity towards non-covalent interactions with the 1,3-dipole) is important since in most cases it influences the regio- and stereochemistry of the cycloaddition.

1.2.3 Mechanistic Issues

Given the importance of the 1,3-dipolar cycloaddition reaction, the elucidation of its mechanism is crucial to understanding the variables that determine its regio- and stereocontrol. Based on kinetic measurements, stereochemical results, and solvent and substituent effects^{16,17} Huisgen and co-workers developed a detailed rationale for the concerted mechanism of the 1,3-dipolar cycloaddition. The proposed model for the transition state of these reactions was of a concerted nature, in which the 4π -electron system interacts with the π -bond of the dipolarophile (Figure 6a). Firestone, on the other hand,¹⁸ presented a variety of challenges to the concerted mechanism postulating that these reactions take place *via* a singlet diradical intermediate (Figure 6b).

a) The Huisgen mechanism

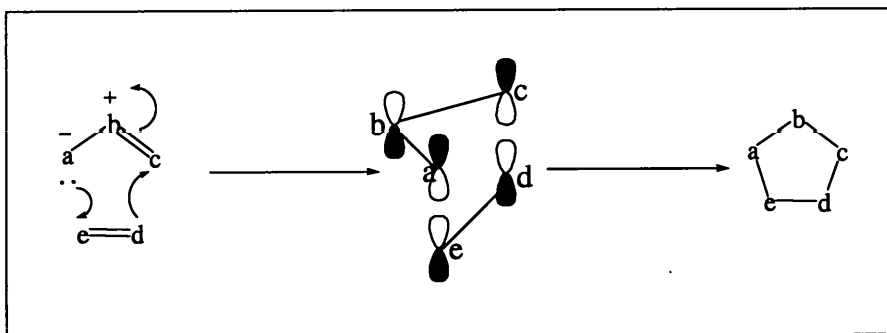


Figure 6a: The Huisgen postulated concerted mechanism

b) The Firestone mechanism

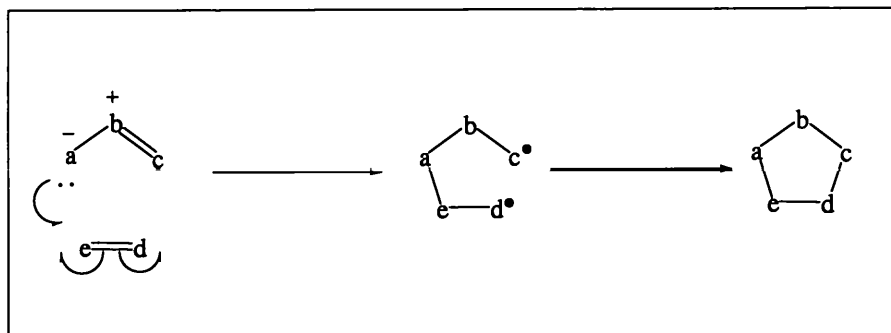
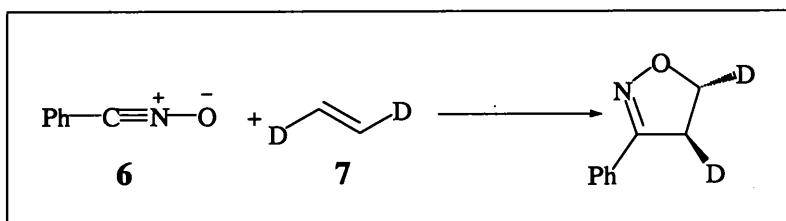


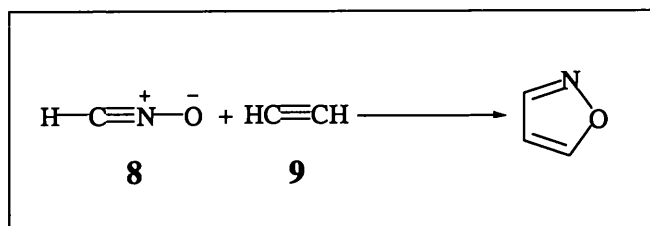
Figure 6b: The Firestone postulated diradical mechanism

In the 1,3-DC reaction between benzonitrile N-oxide **6** and *E*-1,2-dideuterioethene **7** (Scheme 3), where a diradical intermediate would allow a 180° rotation of the terminal bond and would thus be expected to yield a mixture of the *cis* and *trans* isomers, the 4,5-*trans* product was formed in > 98% stereospecificity.¹⁹ Taken together with the work of Houk, who showed that analysis of the concerted mechanism in terms of frontier molecular orbital theory²⁰ could rationalise the regioselectivity of the reaction, this ultimately settled the dispute in favour of the concerted mechanism.



Scheme 3

Ab initio calculations carried out by Komornicki *et al.* on the 1,3-DC of the prototypical nitrile oxide **8** and ethyne **9** (Scheme 4) verified the concerted nature of the reaction.²¹



Scheme 4

1.2.4 Stereochemistry

The high regio- and stereoselectivity of these reactions strongly suggests that the addition of both intervening components takes place *via* a highly ordered transition state. Two possible transition state geometries arise for the reaction between, for example, an azomethine ylide 1,3-dipole and a dipolarophile (Figure 7).

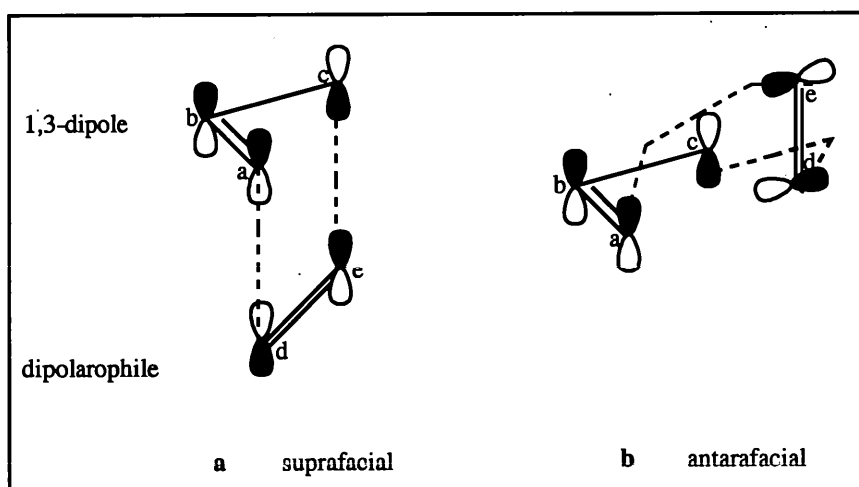


Figure 7: Possible approaches of the dipole and dipolarophile in a 1,3-DC

Theoretical studies support the contention that the 1,3-dipole and the dipolarophile will preferentially approach each other in a *suprafacial* manner,²² where the two new bonds form on the same surface of either particular reactant (Figure 7a). It is evident that this transition state is favourable since overlap of the relevant molecular orbitals is maximised. Naturally, the same degree of orbital overlap is achieved in the situation wherein the 1,3-dipole approaches the dipolarophile from either face.

If, in contrast, one bond is formed on one surface of a reactant and the other bond is formed on the other surface, then the reaction is described as being *antarafacial* (Figure 7b). In this case, effective orbital overlap is much more difficult to achieve and in most cases the 1,3-dipole would have to spatially arrange itself in such a manner that would compromise its π system and hence the allylic resonance. Such reactions are therefore considered to be rare and in 1,3-dipolar cycloadditions the formation of the major product occurs *via* the *suprafacial* approach.

A *suprafacial* approach involving a dipolarophile that contains substituents raises other issues that need to be addressed. First, the dipolarophile may approach the 1,3-dipole with its substituent directly underneath the plane of the latter; this constitutes the *endo* transition state (Figure 8). This transition state may lie on the most energetically favourable pathway if it involves a secondary non-covalent orbital interaction between the 1,3-dipole and the substituent Z that provides extra stabilisation in the transition state. Second, where Z is bulky, steric hindrance constitutes an obstacle to bond formation and therefore the dipolarophile may prefer to approach the 1,3-dipole with its substituent pointing away from the latter; this is called the *exo* transition state (Figure 8). *Exo* and *endo* transition states give rise to products that are diastereomeric (Figure 8).

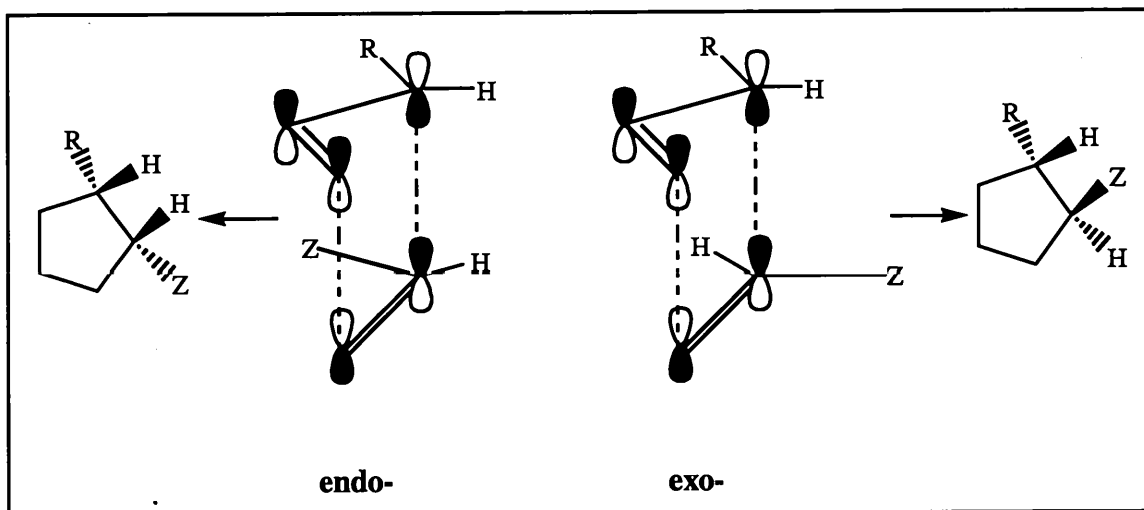


Figure 8: *Suprafacial* transition states for a 1,3-DC reaction

By introducing reagents which are facially discriminated, one can control the way in which the dipolarophile approaches the 1,3-dipole (above or below), or *vice versa*, hence giving rise to a specific stereochemistry in the adducts. Introduction of a substituent R at the 1,3-dipole blocking the approach of the dipolarophile from lower plane of the latter (Figure 9a) leads to a single diastereoisomer **10** due to the approach of the dipolarophile from the non-hindered upper face of the 1,3-dipole. An approach of the dipolarophile from the lower plane is hindered by the substituent, thus compromising the formation of the alternative adduct (Figure 9b).

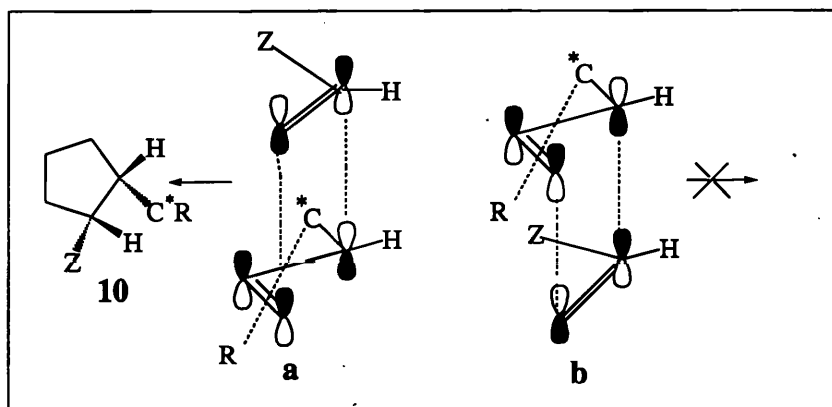


Figure 9: Facially discriminated 1,3-dipoles and stereochemistry of 1,3-DC reaction adducts (*C is a chiral C atom).

1.2.5 Regiochemistry

Frontier molecular orbital theory (FMO) and the principle of conservation of orbital symmetry²³ together offer a coherent mechanistic picture for the 1,3-DC reaction based on a concerted process.

The fundamental assumption of these concepts is that *a majority of chemical reactions should take place at the position of, and in the direction of, maximum overlap of the HOMO (highest occupied molecular orbital) and the LUMO (lowest unoccupied molecular orbital) of the reactant species.*²⁴ The transition state of the concerted 1,3-DC reaction is thus governed by the FMOs (HOMO, LUMO) of the substrates. Thus, either the HOMO of the dipole interacting with the LUMO of the dipolarophile or the LUMO of the dipole with the HOMO of the dipolarophile should control the course of the reaction. Fukui²⁴ reasoned that maximum orbital overlap takes place between orbitals which are separated by the

narrowest energy gap; the narrower the gap the faster the reaction. By calculating the relative energies of these FMOs^{25,26,27} one can predict the dominant FMO interaction and thus often directly predict the preferred regiochemistry of the reaction. Bearing in mind the relative FMO energies between the 1,3-dipole and the dipolarophile, Sustman has classified 1,3-DC reactions into three types (Figure 10)²⁸.

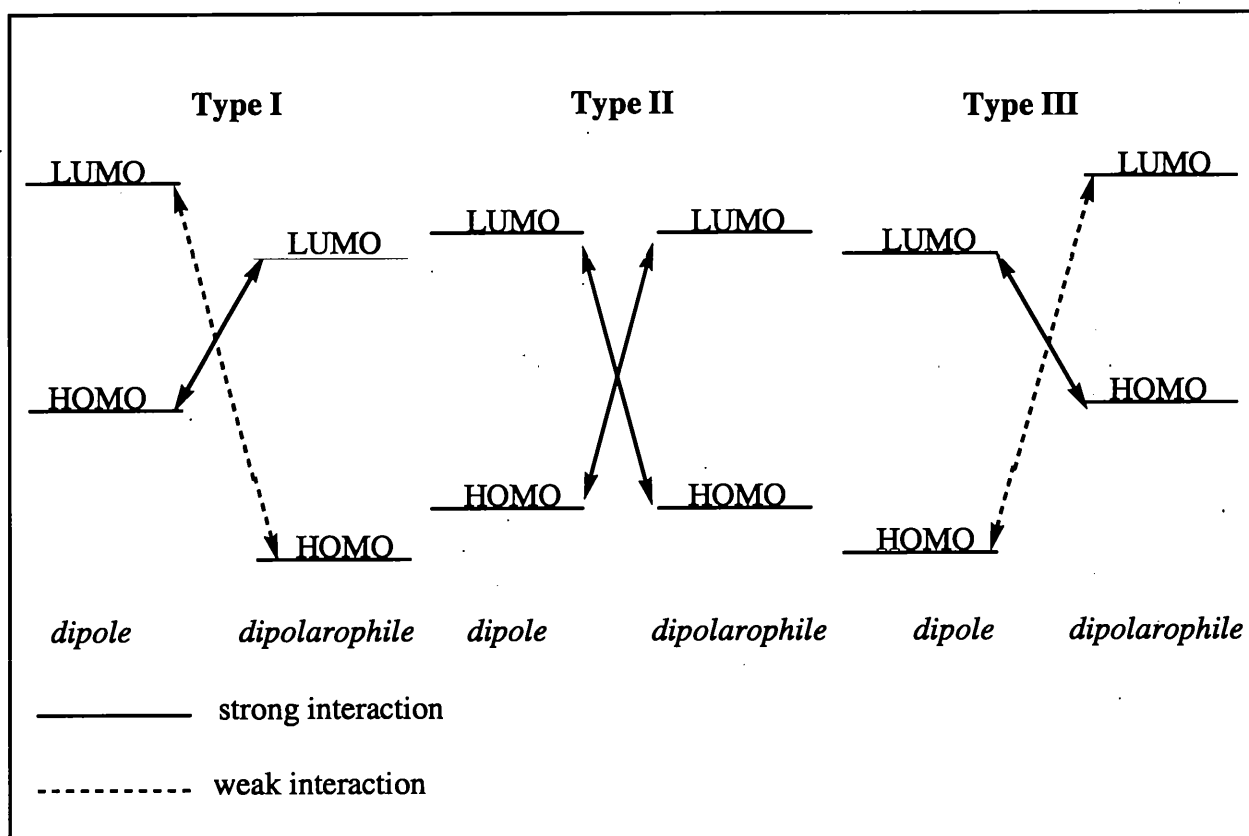


Figure 10: Different types of HOMO-LUMO interaction between 1,3-dipole and dipolarophile.

In type I 1,3-DC reactions the dominant FMO interaction is that of the HOMO of the dipole with the LUMO of the dipolarophile (Figure 10). Azomethine ylides are typical substrates for this type of 1,3-DC reactions. For type II, the similarity of the FMO energies of the 1,3-dipole and dipolarophile implies that both HOMO-LUMO interactions are

significant and thus there is no dominant interaction. Typical substrates for this type of 1,3-DC reaction are nitrones. Finally, for type III we have the case where the dominant FMO interaction is that between the LUMO of the dipole and the HOMO of the dipolarophile. Substrates for this type of 1,3-DC reaction are ozone and nitrous oxide.

Two directions of cycloaddition are conceivable if both the 1,3-dipole and the dipolarophile contain non-identical termini. Consequently, the formation of regioisomeric products is possible (Figure 11).

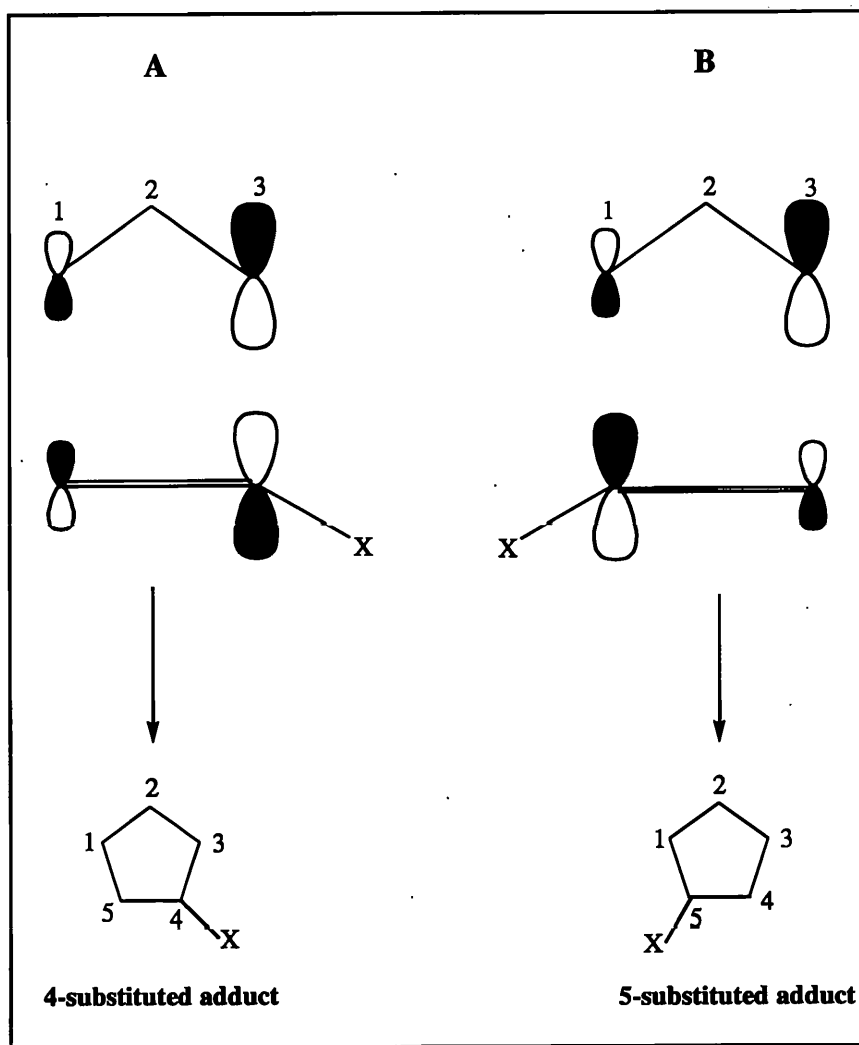


Figure 11: Regiochemistry of the 1,3-DC reaction

The ratio of regioisomers mirrors the ratio of the respective rate constants for the two orientations of cycloaddition; thus regioselectivity becomes an issue associated with reactivity. To determine reactivity and therefore account for the regioselectivity of the 1,3-DC reaction one must assess which type of orbital interaction is dominant; HOMO (dipole) and LUMO (dipolarophile), or LUMO (dipole) and HOMO (dipolarophile) (Figure 10). Having determined which interaction is of primary importance, focus shifts to the coefficients of the relevant orbitals. Consider a reaction that is dipole-HOMO controlled, *i.e.* type I (Figure 11). The relevant orbitals coefficients are then those of the dipole-HOMO and the dipolarophile-LUMO. The regioselectivity of the reaction is then expected to be that which maximises the size of the wave functions of the overlapping orbitals during bond formation. Maximum overlap of the relevant molecular orbitals and matching of the magnitude of the orbital coefficients, *i.e.* large (dipole) with large (dipolarophile) and small (dipole) with small (dipolarophile), is achieved in example A (Figure 11), giving rise to the 4-substituted adduct. The alternative case B, however, despite the fact that the molecular orbitals are appropriately phased for overlap, the magnitudes of the orbital coefficients involved do not match and this represents the formation of the less favourable 5-substituted regioisomer, which would constitute a minor product.

1.3 Azomethine ylides as 1,3-dipoles

Within the frame-work of 1,3-dipoles as defined by Huisgen,¹⁴ azomethine ylides belong to the class of azomethinium betaines, and there are acyclic and cyclic examples of these (Figure 12).

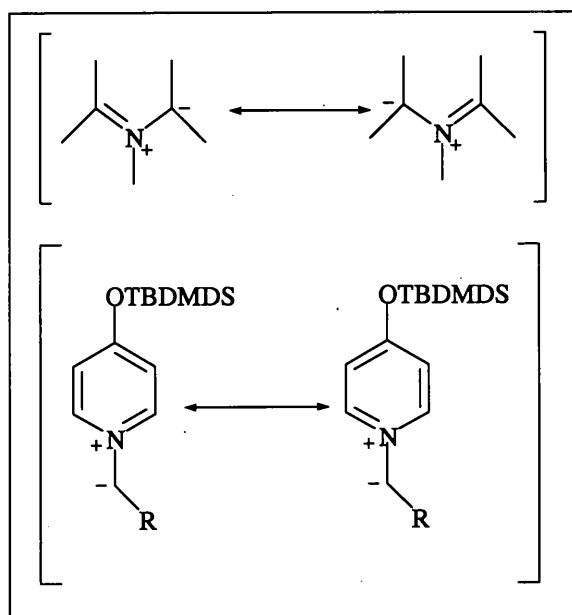


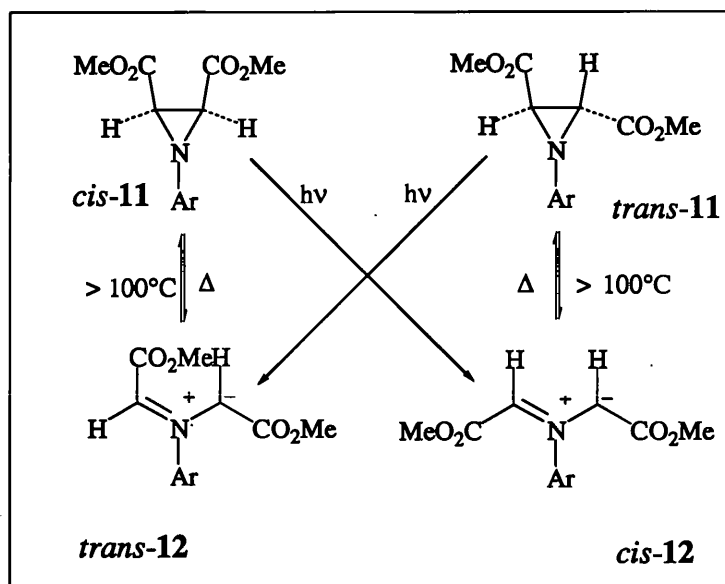
Figure 12: Acyclic and cyclic azomethine ylides.

It has been shown experimentally that azomethine ylides show low reactivity with simple alkene dipolarophiles. However, cycloadditions involving such ylides are accelerated both by electron-donating or conjugating groups within the dipole, as these raise the energy of its HOMO, and by electron-withdrawing or conjugating groups in the dipolarophile, as these lower the LUMO of the latter.^{28,29}

1.3.1 Generation of azomethine ylides

Azomethine ylides are unstable species, so they are prepared *in situ* in low concentration and trapped directly by added dipolarophiles.¹⁴ There are several methods for the generation of azomethine ylides; only a selection will be discussed here, arranged according to precursor functional group.

Conrotatory thermolysis and disrotatory photolysis



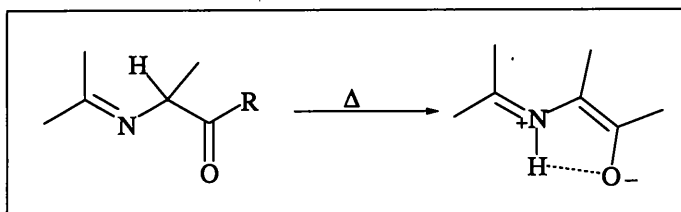
Scheme 5

In 1967 Huisgen and co-workers reported the electrocyclic ring-opening by thermolysis and photolysis of the stereoisomeric aziridines, **cis-11** and **trans-11**, to afford stereochemically distinct azomethine ylides, **trans-12** and **cis-12**, which were then trapped *in situ* by dipolarophiles.³⁰ Thermal conrotatory ring opening of **cis-11** afforded **trans-12** whereas thermal conrotatory ring opening of **trans-11** afforded **cis-12** (Scheme 5).

Disrotatory photolytic ring opening of *cis*-11 afforded *cis*-12 whereas disrotatory photolytic ring opening of *trans*-11 afforded *trans*-12. Although the yields of the direct disrotatory photolysis were not as high as those obtained during thermolysis (81-84%), very reasonable yields (69%) of the adduct were obtained using this process. A limitation of this methodology is that ring-opening of aziridines only works well when the substituent groups are capable of stabilising the dipole centres, failing completely when simple alkyl substituents are used.

Imines

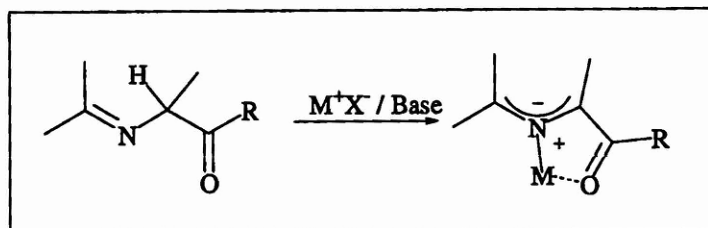
a) Isomerisation



Scheme 6: Thermal isomerisation of an imine to form an azomethine ylide

This method involves isomerisation of an imine derivative of an α -aminoester containing an enolisable hydrogen, to yield the azomethine ylide (Scheme 6) which can then be trapped by reaction with the appropriate dipolarophile.³¹

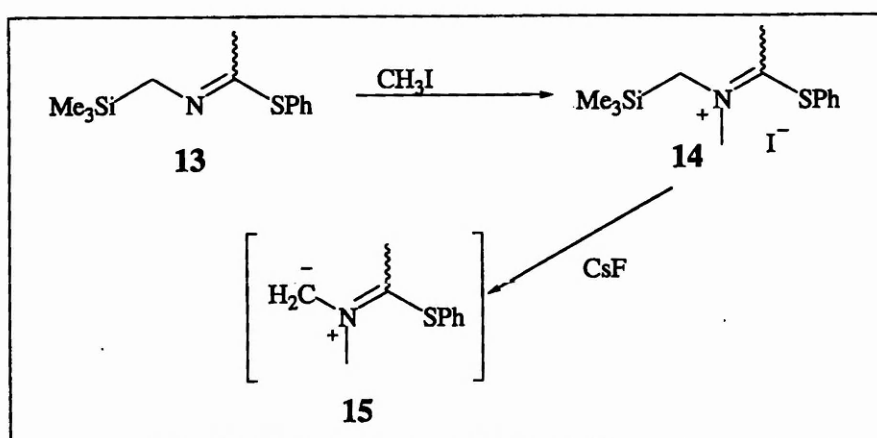
b) N-metalation



Scheme 7: Generation of azomethine ylides through N-metalation

An imine derivative of an α -aminoester containing an enolisable hydrogen can also be readily transformed into the N-metalated azomethine ylide by an appropriate metal salt ($M^{n+} = \text{Ag, Tl, Li, Mg, Mn}$) in the presence of base (Scheme 7).³²⁻³⁴ This kind of reaction has proved to be remarkably efficient in its possible asymmetric versions³⁵ and in addition the reaction tolerates a wide range of substituents and is therefore well suited for combinatorial synthesis.³⁶

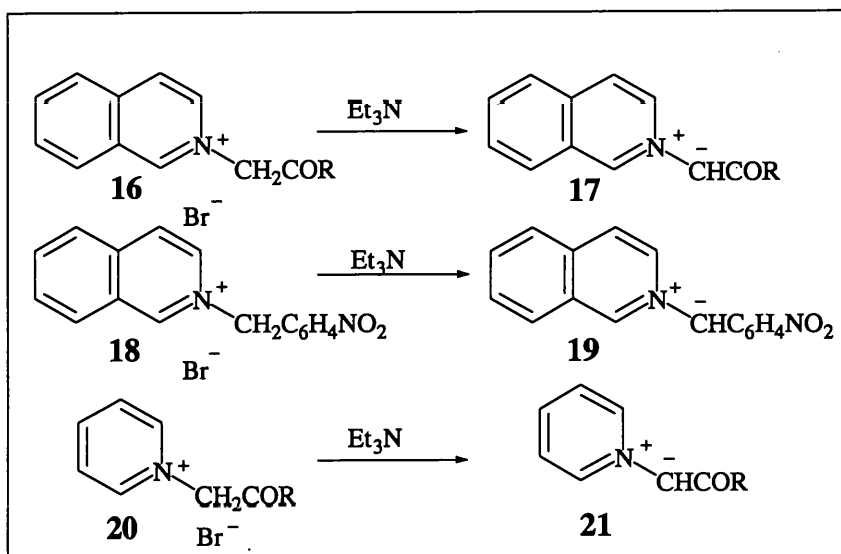
c) Desilylation



Scheme 8: Desilylation of imines as a method for generation of azomethine ylides

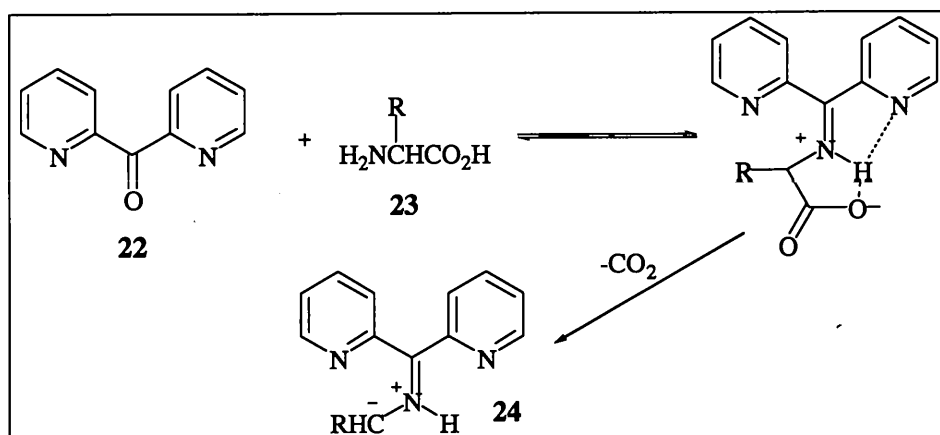
Vedejs and co-workers have pioneered this approach³⁷ and it has proved to be an efficient and widely used methodology for generation of azomethine ylides. Treatment of **13**, for example, with one equivalent of iodomethane (CH_3CN , 25°C , 16 hours) affords the N-alkylated intermediate **14**, which, upon addition of caesium fluoride, generates the azomethine ylide **15** (Scheme 8).³⁸

Pyridinium and similar salts



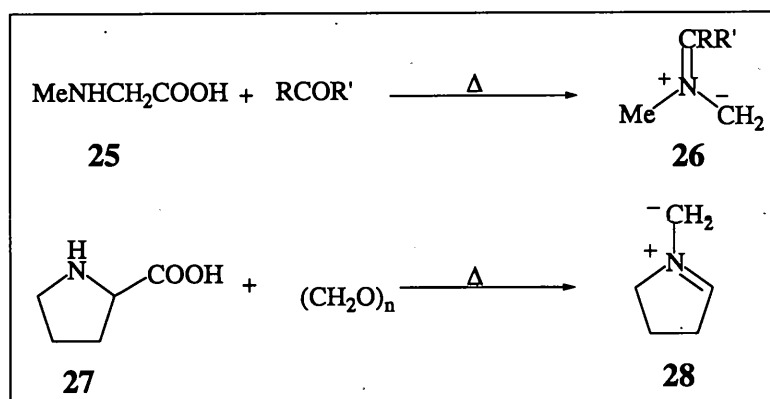
Scheme 9: Imonium and pyridinium salts as azomethine ylide precursors

A general route based on this approach is the deprotonation of isoquinolinium salts **16**, **18** and the pyridinium salt **20**. The azomethine ylides **17**, **19** and **21** retain the ability to undergo addition even though the $\text{C}=\text{N}$ bond is an integral part of the heteroaromatic ring.



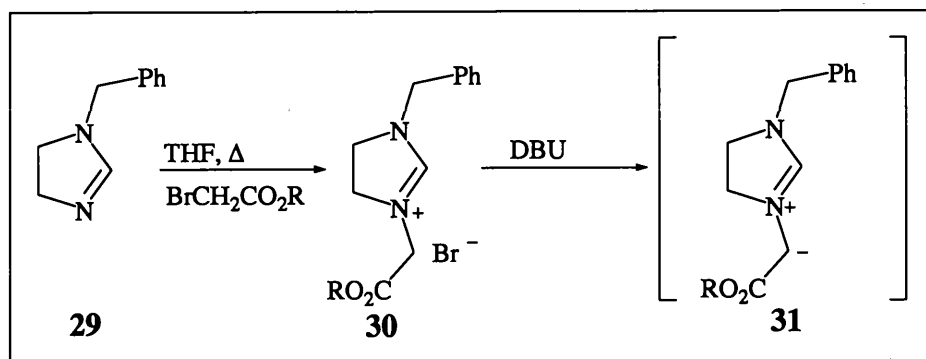
Scheme 10: Generation of azomethine ylide using α -amino acids

Aldehydes and ketones react with α -amino acids, or more generally with primary amines, to form imines (Schiff bases). Condensation of the 2,2'-bipyridyl ketone **22** with α -amino acids such as **23** yields an imine that upon decarboxylation gives rise to the azomethine ylide **24** (Scheme 10).³⁹ This chemistry has been successfully extended to *N*-substituted acyclic and cyclic amino acids, **25** and **27** respectively, which afford the acyclic **26** and cyclic **28** azomethine ylides, respectively (Scheme 11).^{40a}



Scheme 11: Azomethine ylides from *N*-substituted acyclic and cyclic amino acids.

Amidines



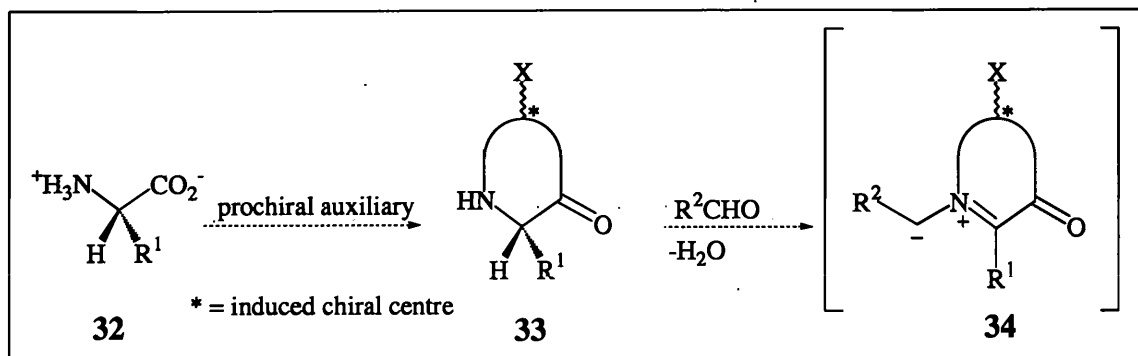
Scheme 12: Amidines as azomethine ylide precursors

The use of amidines as a source of azomethine ylides has developed enormously over the past 20 years.^{38,40b} Previous researchers in our group have developed a very elegant and efficient methodology to access azomethine ylides generated from heterocyclic amidines, such as 1-benzyl-4,5-dihydroimidazole **29**.⁴¹ This cyclic amidine is N-alkylated using a bromoacetate ester to afford the salt **30** that, upon deprotonation with an appropriate base (diazabicyclo[5.4.0]undec-7-ene, DBU), generates the azomethine ylide **31** (Scheme 12) which can be trapped with a suitable dipolarophile to afford hexahydropyrrolo[1,2-*a*]imidazoles.⁴²

1.3.2 Generation of chiral azomethine ylides

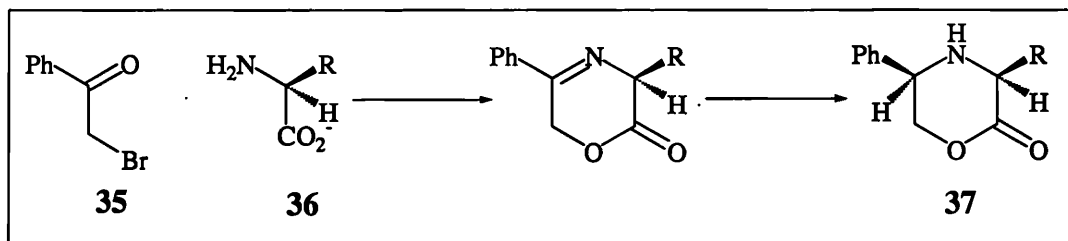
Despite there being a variety of routes to form azomethine ylides, methods for the generation of chiral azomethine ylides are continually sought. For instance, although azomethine ylides can be accessed from α -amino acids and their condensation with

aldehydes or ketones (Section 1.2.1), the chirality at the α -centre is necessarily lost in the process of ylide generation. Consequently, Harwood and co-workers proposed the use of a chiral template *en route* to chiral azomethine ylides from α -amino acid precursors (Scheme 13).⁴³



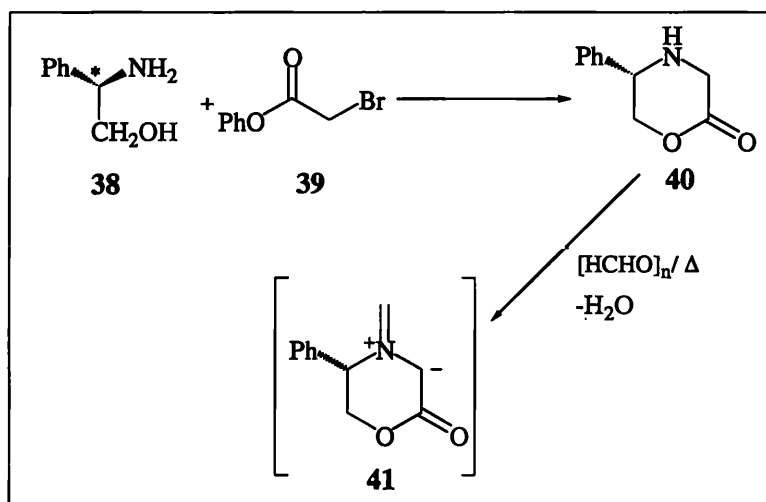
Scheme 13: The use of a prochiral auxiliary in the generation of chiral azomethine ylides

The chirality of the amino acid **32** is used to set up a new chiral centre in intermediate **33**. Upon reaction with an appropriate aldehyde, followed by loss of water, this intermediate affords a chiral azomethine ylide **34** despite the loss of chirality at the original amino acid centre. Development of this concept was supported by earlier workers, such as Williams who described the use of (5*R*, 6*S*)-diphenylmorpholine as an azomethine ylide precursor,⁴⁴ and also by Caplar who demonstrated that hydrogenation of the cyclic condensation products derived from α -bromoacetophenone **35** and α -amino acids **36** occurs stereospecifically to form homochiral 3-substituted-5-phenylmorpholinones with a total transfer of chirality from the α -amino acid centre to the newly formed benzylic centre in the product **37** (Scheme 14).⁴⁵



Scheme 14: Chiral phenylmorpholinones as potential chiral azomethine ylide precursors

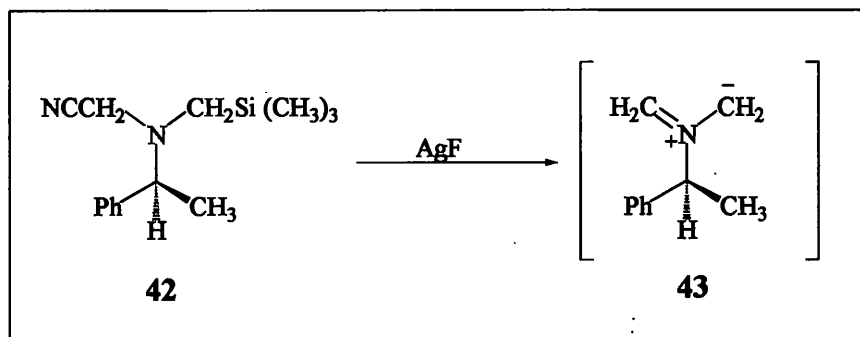
Harwood was then able to demonstrate that reaction of (*R*)-5-phenylmorpholinone **40**, synthesised from (*R*)-2-phenylglycinol **38** and phenyl bromoacetate **39**, with an appropriate aldehyde afforded the desired chiral azomethine ylide **41** that could be trapped *in situ* with a variety of alkene dipolarophiles (Scheme 15).⁴³



Scheme 15: Chiral azomethine ylides based on chiral morpholinone templates.

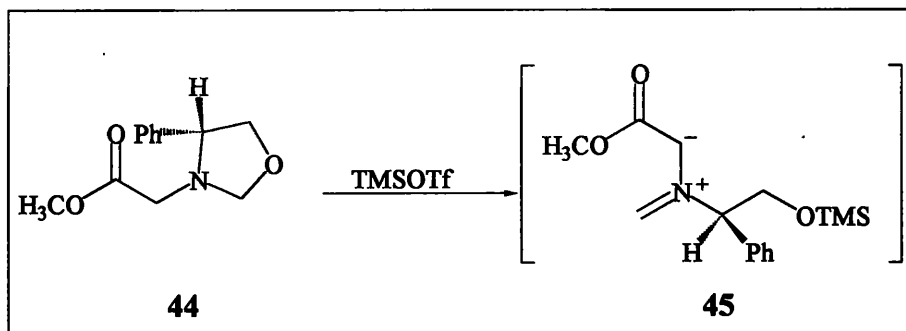
Using a different approach, Padwa and co-workers accessed chiral azomethine ylides by reaction of chiral *N*-cyanomethyl-*N*-trimethylsilylmethylamines **42** with silver fluoride (Scheme 16).⁴⁶

Using a different approach, Padwa and co-workers accessed chiral azomethine ylides by reaction of chiral *N*-cyanomethyl-*N*-trimethylsilylmethylamines **42** with silver fluoride (Scheme 16).⁴⁶



Scheme 16: Chiral azomethine ylides from *N*-cyanomethyl-*N*-trimethylsilylmethylamines.

A somewhat different, yet interesting and efficient, approach towards the generation of chiral azomethine ylides was adopted by Husson and co-workers⁴⁷ who used the chiral oxazoline **44** as a chiral azomethine ylide precursor (Scheme 17).



Scheme 17: Chiral oxazolines as precursors to chiral azomethine ylides

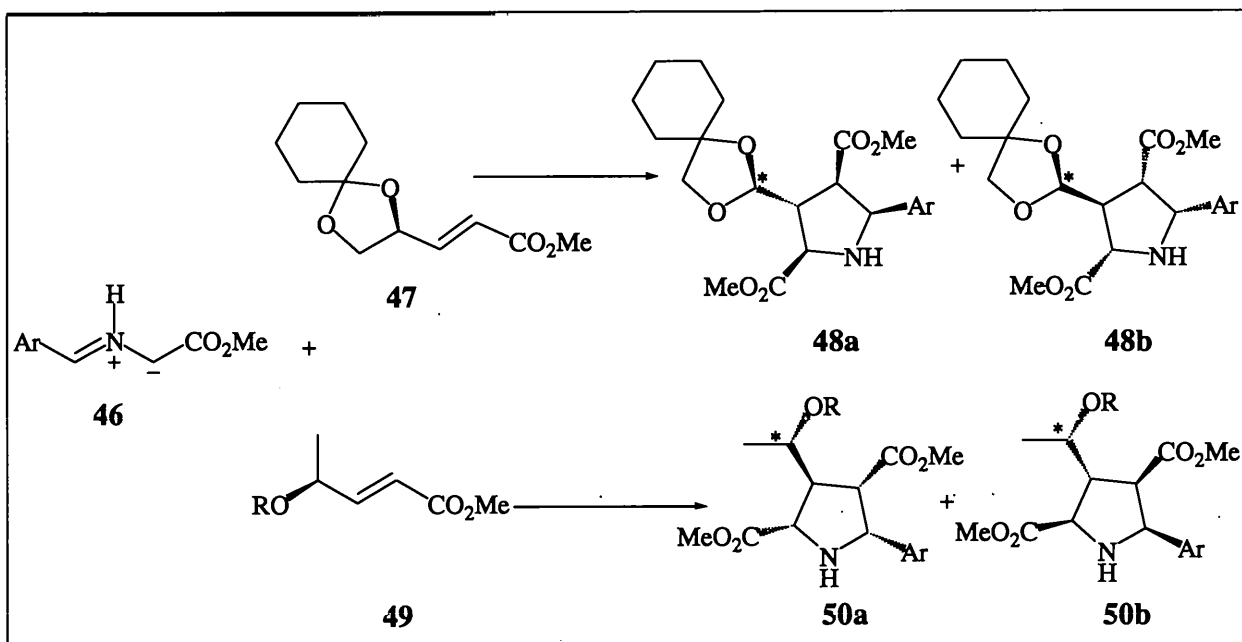
1.3.3 1,3-Dipolar cycloaddition of azomethine ylides

The 1,3-DC reactions of azomethine ylides are very well documented and widely studied.^{4,5} In particular, the assembly of biologically relevant heterocycles such as pyrroles, pyrrolidines and pyrrolizidines has been well recognised.^{11,48,49}

An earlier report of a 1,3-DC reaction of an azomethine ylide to afford a pyrrolidine ring was by Vedejs and co-workers in 1979.³⁷ Since then a tremendous amount of work has been reported on this area,⁵⁰ perhaps not so surprising since the pyrrolidine ring is a frequently encountered structural unit of many synthetically challenging alkaloids.⁵¹

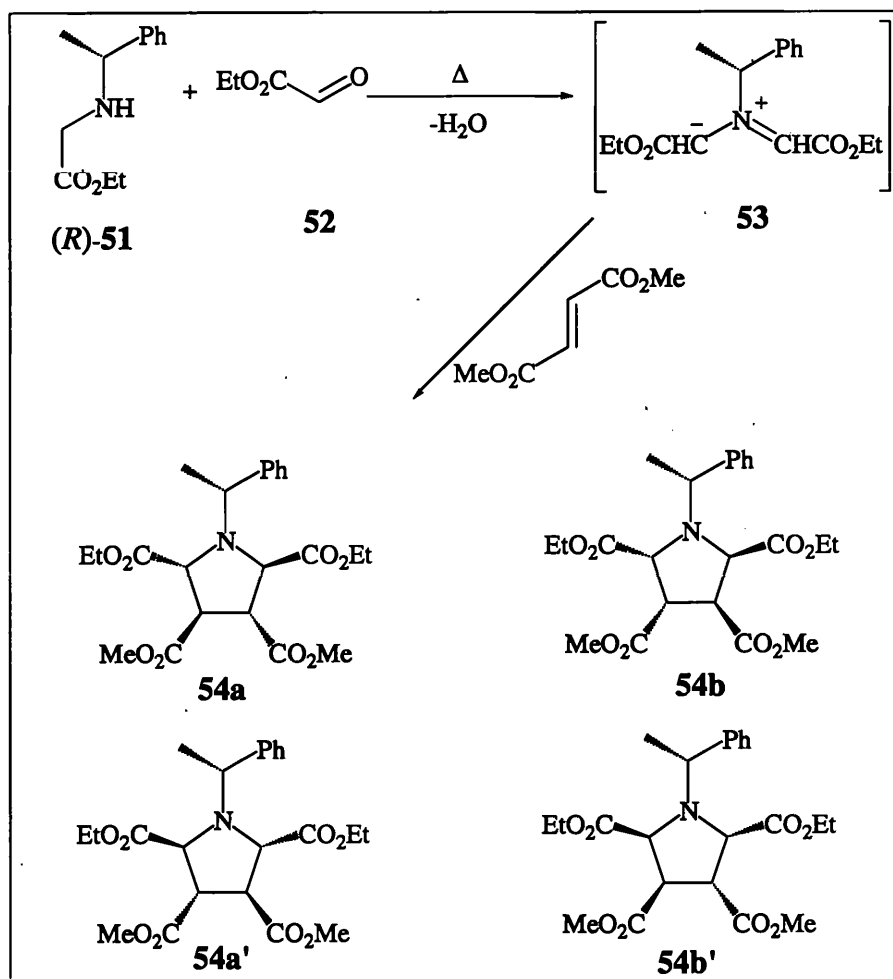
Annunziata *et al.* reported the 1,3-DC reaction of azomethine ylides **46** with (E)- γ -alkoxy- α , β -unsaturated esters **47** and **49** to afford substituted pyrrolidine rings (Scheme 18).³⁵

In each case, the 1,3-DC reaction afforded a single regioisomer as a diastereomeric pair, **48a/48b** and **50a/50b**, respectively.



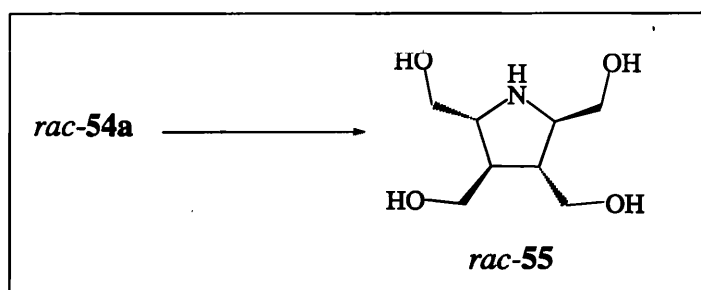
Scheme 18: Tetrasubstituted pyrrolidines from a 1,3-DC reaction of an azomethine ylide

The synthesis of polyfunctionalised pyrrolidine ring derivatives using the 1,3-DC reaction of azomethine ylides constitutes a very active and rich research area. Reported examples of such reactions are very numerous, therefore only one interesting example will be discussed here. Using the common knowledge that azomethine ylides can be generated from the condensation of α -amino acids with aldehydes (Scheme 10), Risch and co-workers devised a route to tetrakis(alkoxycarbonyl) substituted pyrrolidines (Scheme 19).⁵²



Scheme 19: Polyfunctionalised pyrrolidines by 1,3-DC reaction of azomethine ylides

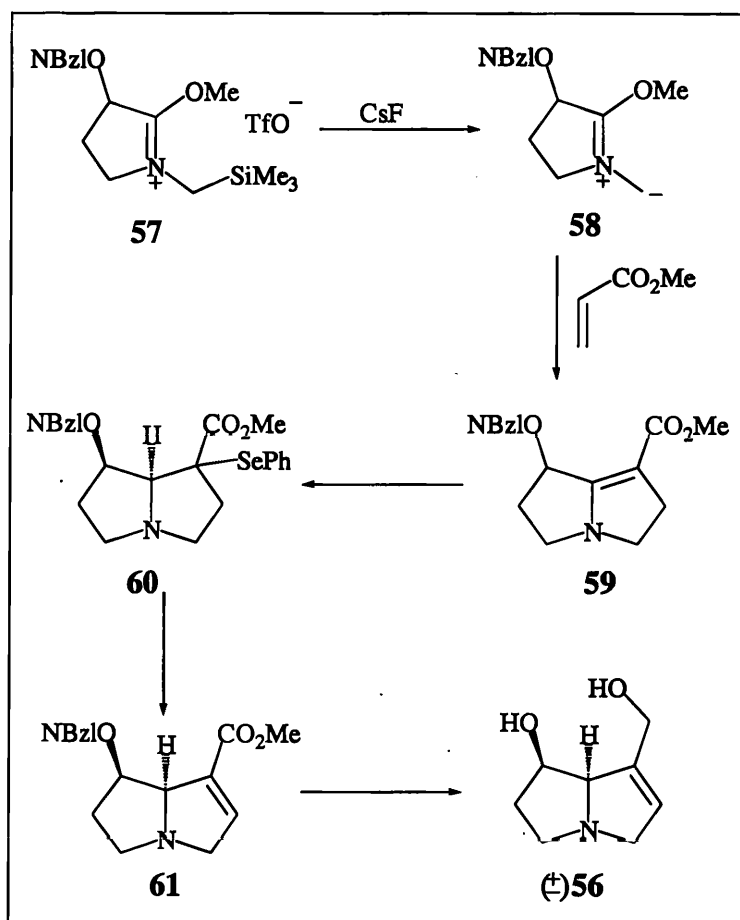
Reaction of ethyl *N*-(1-phenylethyl)aminoacetate **51** with ethyl glyoxalate **52** led to the generation *in situ* of the chiral azomethine ylide **53** which, upon reaction with dimethyl fumarate, afforded the *exo*-cycloadducts **54a** and **54a'** and the *endo*-cycloadducts **54b** and **54b'**. These pyrrolidine adducts showed potential as precursors for new chiral auxiliaries due to their C₂ axis of symmetry. Reduction of the pyrrolidine *rac*-**54a** by lithium aluminium hydride, followed by debenzylation with H₂-Pd/C (10%) in ethanol afforded the 2,3,4,5-tetrahydroxymethylpyrrolidine *rac*-**55** in good yield (Scheme 20).



Scheme 20: Tetrahydroxymethylpyrrolidine *rac*-**55**

Five membered cyclic azomethine ylides are a powerful synthetic tool in the synthesis of tricyclic heterocycles rings such as pyrrolizidines.^{53,54} A classic example of this type of 1,3-DC reaction is the synthesis of racemic retronecine **56** (Scheme 21) by Vedejs and co-workers,⁵⁵ using the desilylation methodology discussed earlier. Conversion of the salt **57** to the cyclic azomethine ylide **58** was achieved by treating the former with anhydrous CsF. Addition of methyl acrylate to the azomethine ylide generated *in situ* afforded the pyrrolizidine derivative **59**. Reduction of **59** with diisobutylaluminium hydride (DIBAL-H) was followed by trapping the aluminium enolate using PhSeCl to afford **60**. Oxidation (*m*-

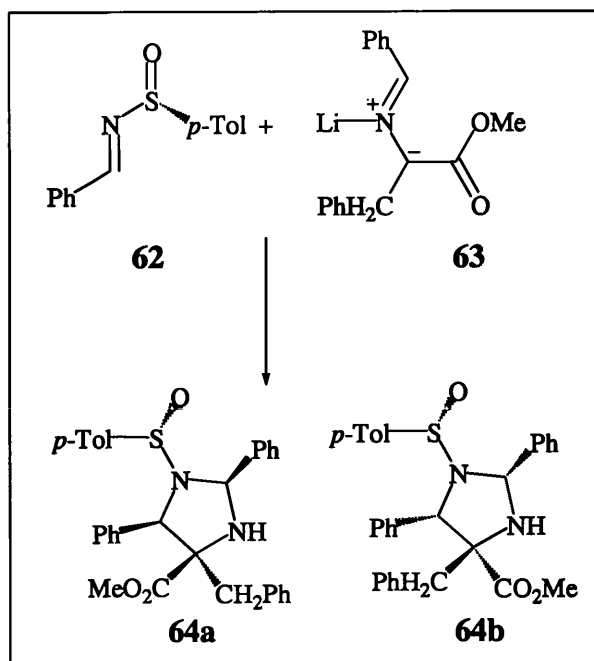
CPBA) and thermal elimination of PhSeOH afforded **61** which was subsequently reduced using Dibal and deprotected to afford racemic retronecine **56**.



Scheme 21: Synthesis of retronecine **56** using 1,3-DC of an azomethine ylide

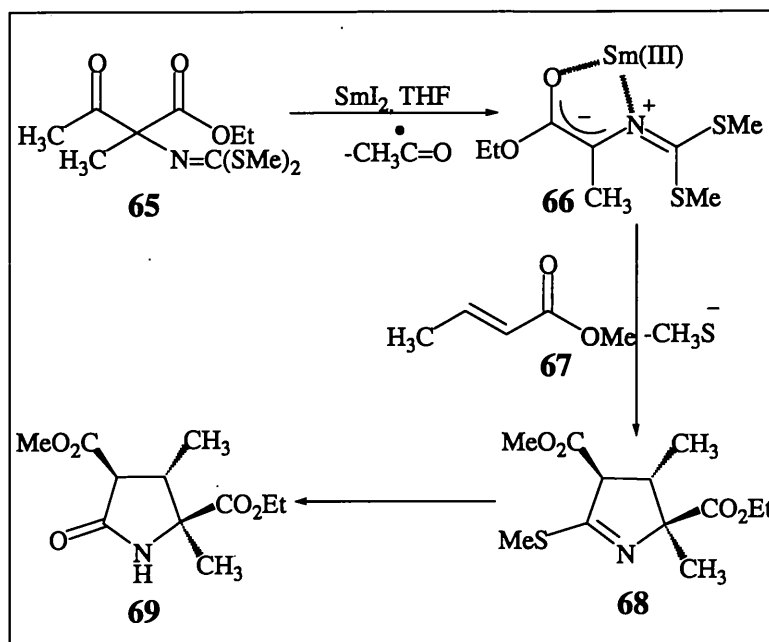
The 1,3-DC reactions of azomethine ylides with dipolarophiles bearing heteroatoms such as sulfur as substituents have also proved to be of great synthetic utility, for example *en route* to imidazolidine derivatives (Scheme 22). In most cases these reactions appear to be highly diastereoselective producing adducts with a degree of enantiopurity since the sulfinimine substrates display an excellent facial selectivity upon reaction with various dipoles. For example, **64a** and **64b** are formed as a 95:5 mixture of diastereoisomers. Thus,

they constitute potential precursors to chiral imidazolidines, as reported by Viso and co-workers (Scheme 22).⁵⁶



Scheme 22: 1,3-DC reaction of sulfinimines with azomethine ylides

En route to pyroglutamates, Ibarra and co-workers have used Sm(III)-azomethine ylides as 1,3-dipoles.⁵⁷ Due to the high coordination number of this cation,⁵⁸ which should favour tightly coordinated reaction intermediates, high diastereoselectivities in the cyclisation process could be expected (Scheme 23). Treatment of ketone **65** with SmI₂ leads to the formation of ylide **66** through a reductive deacetylation. Cycloaddition of the latter with ester **67** leads to **68** which affords pyroglutamate **69** in a *de* (diastereomeric excess) of 80% upon acid hydrolysis.



Scheme 23: 1,3-DC reaction of Sm (III)-azomethine ylides

The application of 1,3-DC reactions of azomethine ylides in natural product chemistry is significant. For example, marine natural products known as lamellarins, and in particular lamellarin K **70** (Figure 13), have unusually high potency in the treatment of multi-drug resistant tumours. Not surprisingly, the total synthesis of these natural products has been attempted.⁵⁹

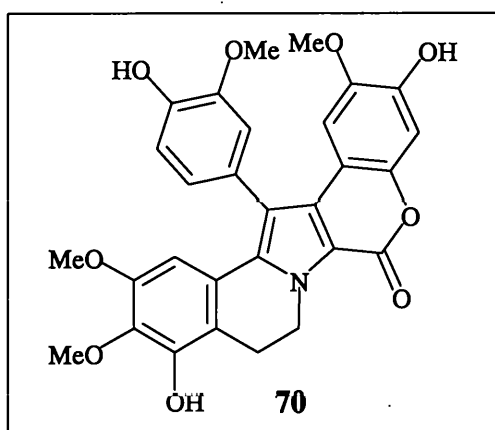
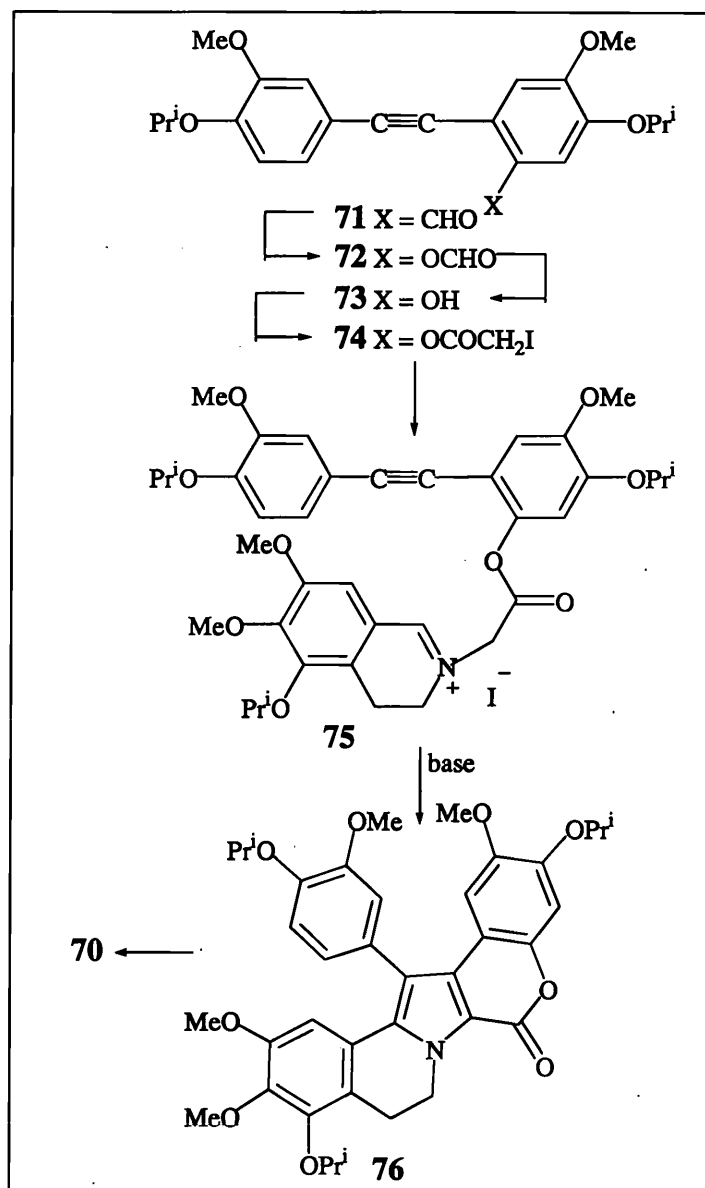


Figure 13: Lamellarin K

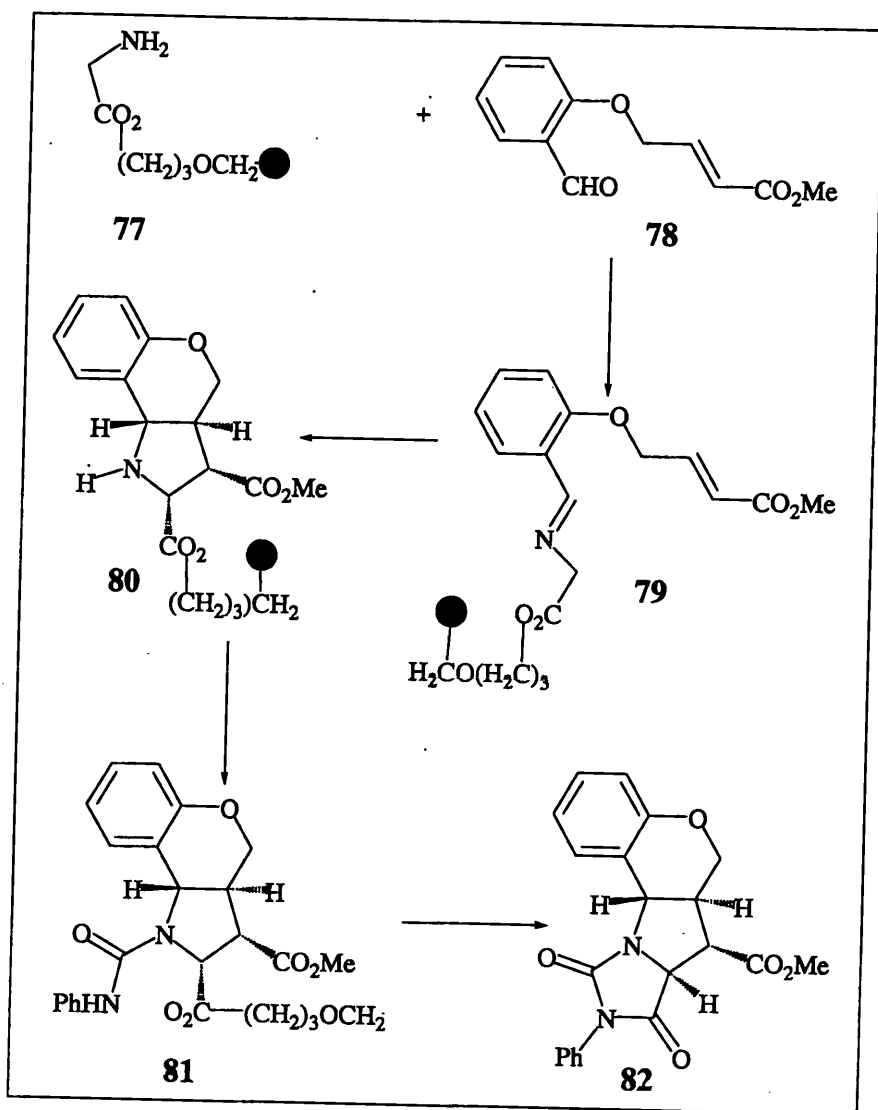
The pivotal step adopted by Banwell and co-workers in their approach to the lamellarin ring system involves the construction of the central pyrrole moiety *via* an intramolecular 1,3-DC reaction of an isoquinoline-based azomethine ylide to a suitable tethered tolane (Scheme 24).⁶⁰



Scheme 24: Synthesis of Lamellarin K by 1,3-DC reaction of azomethine ylides

Thus iodoacetate **74** was reacted with 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline to afford the salt **75**. This was not isolated but immediately treated with Hunig's base to afford the corresponding azomethine ylide. Intramolecular cycloaddition followed by *in situ* aromatisation took place to give lamellarin K triisopropyl ether **76**, which upon three-fold deprotection with an excess of AlCl_3 afforded lamellarin K **70**.

Solid-phase synthesis of polyfunctional heterocyclic targets has also proved to be yet another area of synthetic chemistry wherein the use of the 1,3-DC reaction of azomethine ylides plays a major role. *En route* to the synthesis of hydantoin-containing heterocycles,^{61,62} Kurth and co-workers have reported the solid-phase synthesis of hexahydro-1*H*-pyrrolo[1,2-*c*]imidazoles **82** using the 1,3-DC reaction approach (Scheme 25).³⁶ Triethyl orthoformate-mediated condensation of solid-supported amino ester **77** with aldehyde species **78** afforded **79** as the azomethine ylide precursor. Intramolecular 1,3-DC reaction of the latter gave the solid-phase bound proline derivative **80**. Treatment of the latter with phenyl isocyanate afforded carbanilide **81**. Hydantoin formation and concomitant release of product from the resin afforded pyrroloimidazole **82** in 13 % overall yield (Scheme 25).

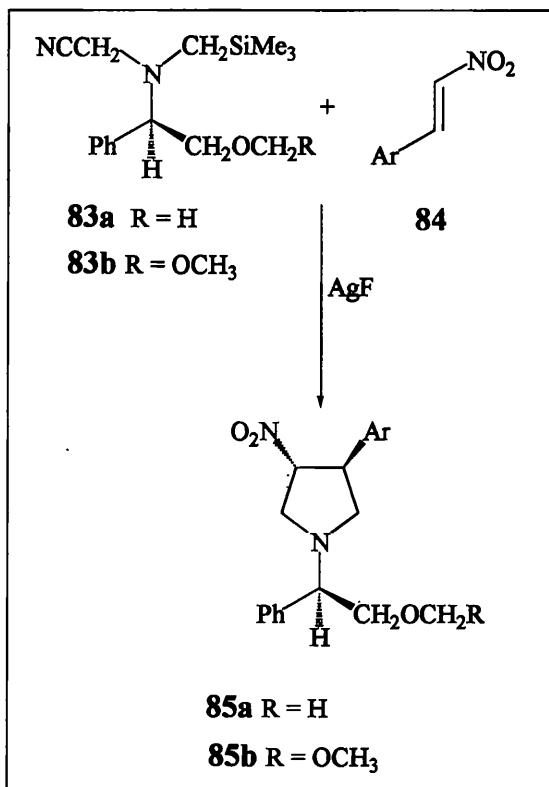


Scheme 25: Solid-phase synthesis using the 1,3-DC reaction of azomethine ylides

1.3.4 Chiral induction by the 1,3-dipole

The availability of chiral azomethine ylides constitutes an important tool in asymmetric synthesis due to their potential to induce enantio- and diastereoselectivity in 1,3-DC reactions. In 1985, Padwa *et al.* published the first report of diastereoselectivity in 1,3-DC reactions of chiral azomethine ylides with a range of dipolarophiles leading to

optically active adducts.⁴⁶ Reaction of the azomethine ylide precursor **83a** with the β -nitrostyrene **84** afforded the adduct **85a** in 20% *de*, whereas precursor **83b** afforded the adduct **85b** with a *de* of 60% (Scheme 26).⁴⁶



Scheme 26: 1,3-DC reaction using a chiral azomethine ylide template

To account for the observed diastereoselectivity two different conformations of the azomethine ylide were considered, **86a** and **86b**. The approach of the dipolarophile toward conformation **86a** is to the face *anti* to the phenyl group, for the obvious steric reasons, while *anti* attack of the dipolarophile to **86b** arises from the approach of the latter to the opposite face of the 1,3-dipole (Figure 14).

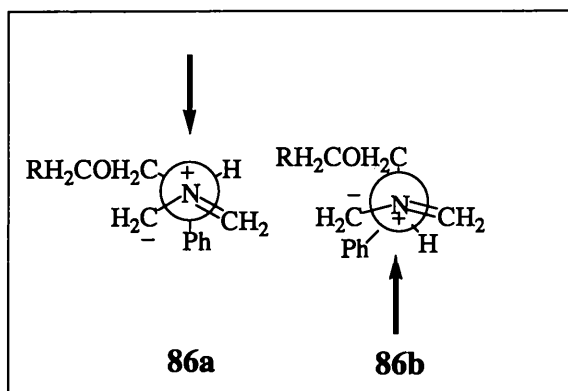
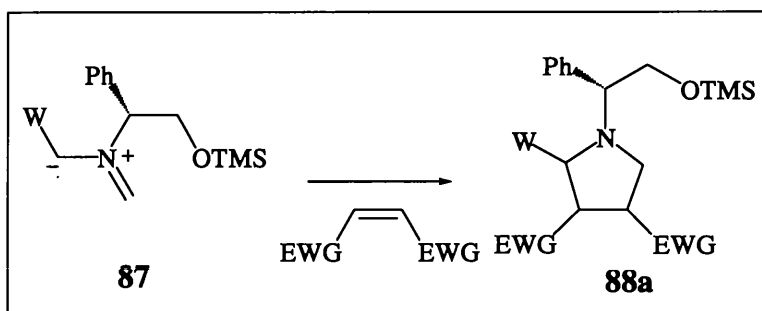


Figure 14: Possible conformations of the azomethine ylide derived from **83b**.

In a series of papers, Husson *et al.* have investigated the 1,3-DC reaction of electron-deficient dipolarophiles with chiral azomethine ylides **87** (Scheme 27).^{47, 63, 64}



Scheme 27: 1,3-DC reaction of chiral azomethine ylides with electron-deficient alkenes

In the reaction of **87** ($W = \text{CN}$) with *N*-phenylmaleimide, four adducts were isolated (the major diastereoisomer in 41% yield), whereas **87** ($W = \text{CO}_2\text{Et}$) gave two isomers in nearly equal amounts. This reaction was further investigated by introducing a menthyl ester as the *W* substituent in **87**. Using this chiral azomethine ylide, only the *exo* product **88b** (Figure 15) was obtained with a *de* > 95%.

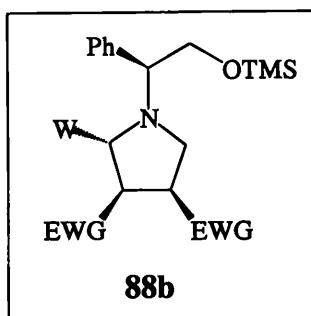
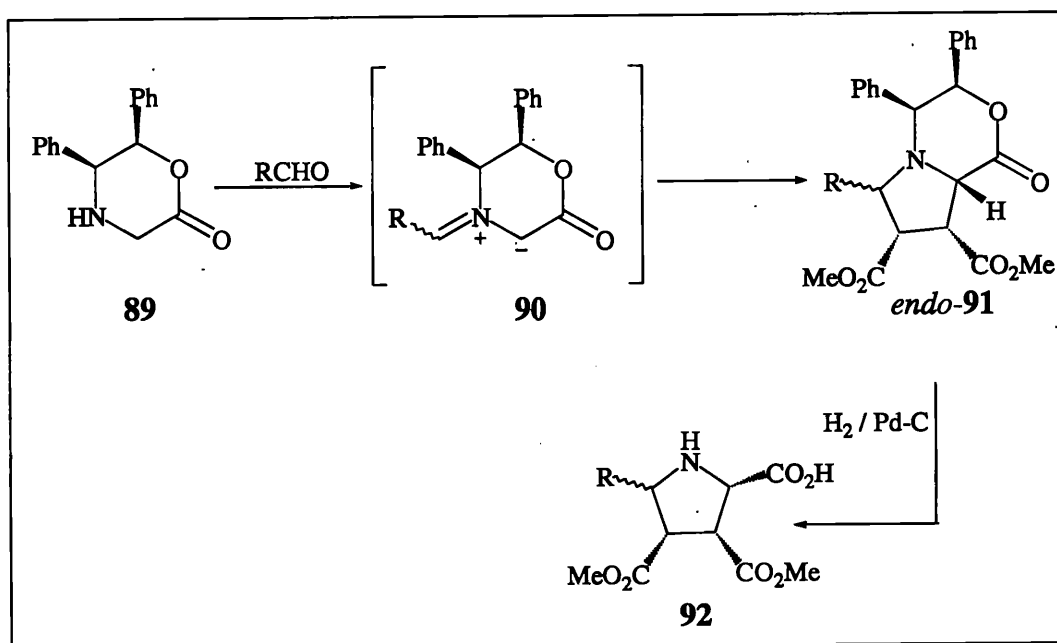


Figure 15: *Exo* adduct for reaction depicted in Scheme 27 (W = menthyl ester)

Chiral azomethine ylides **90** have been used in 1,3-DC with dimethyl maleate (Scheme 28).⁴⁸



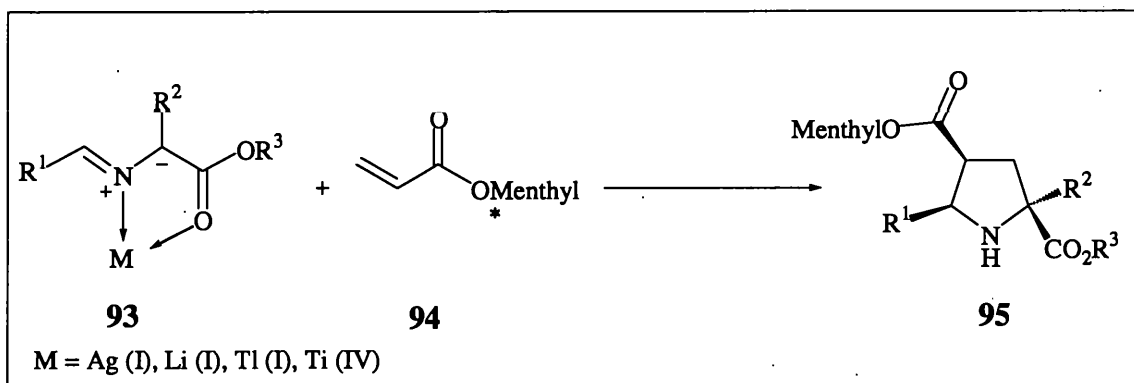
Scheme 28: Chiral azomethine ylides from oxazin-2-ones and their 1,3-DC reaction

In the case when higher aliphatic and aromatic aldehydes were employed in ylide formation, the *endo* selectivity in the 1,3-DC reaction was excellent but the stereoselectivity at the C-6 position of **91**, i.e. the carbon atom arising from the aldehyde

carbonyl carbon atom, was generally low due to *syn-anti* interconversion of the R substituent in **90**. However, as an exception, 2-methylpropanal gave selectively a single diastereoisomer **91** (R = *i*-Pr) in the reaction. The 1,3-DC reaction products **91** could be converted into the corresponding pyrrolidines **92** in high *ee* (enantiomeric excess).⁴⁸

1.3.5 Chiral induction by the dipolarophile

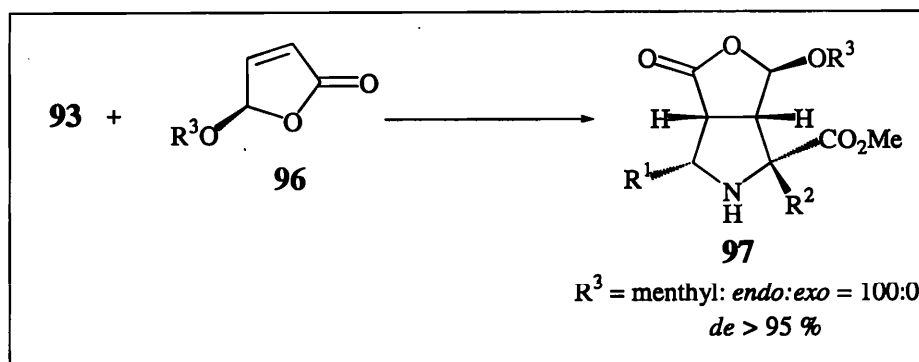
An extensive study was accomplished by Grigg and co-workers, who reacted a series of metalloazomethine ylides, **93**, with electron-deficient dipolarophiles, e.g. menthyl acrylate **94**, to afford 1,3-DC product **95** in good yield, with high *endo* and diastereofacial selectivity induction and with *de* up to > 95% (Scheme 29).^{32, 65-72}



Scheme 29: 1,3-DC reaction of metalloazomethine ylides with chiral dipolarophiles

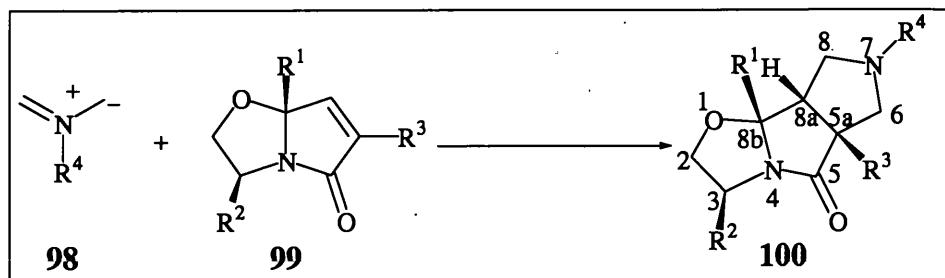
The reaction of azomethine ylides with menthyl acrylate is significantly slower compared with the analogous reaction of methyl acrylate, often leading to lower yields due to a slow metal ion-induced hydrolysis of the imine in the presence of traces of water. However, this

can be overcome by the addition of a base, and the stronger the base the faster the reaction.^{66, 67} The mechanism of the 1,3-DC reaction of these metalloazomethine ylides has been studied extensively. X-Ray diffraction studies of representative cycloadducts has revealed that the absolute configuration of the pyrrolidine stereocentres is independent both of the metal salt and the size of the C-2 substituent. Related work, involving reaction of the metalloazomethine ylides **93** with chiral dipolarophiles such as 2,5-dihydro-5-oxymethylfuran-2-one **96** (R^3 = menthyl) afforded 1,3-DC adduct **97** with complete regioselectivity and *endo* selectivity and with > 95% *de* via the *syn* dipoles, i.e. R^1 is on the same face of the imine functionality in **93**, (Scheme 30).^{66,73} The preferred base proved to be 2-*tert*-butyl-1,1,3,3-tetramethylguanidine > DBU > Et₃N.



Scheme 30: 1,3-DC of metalloazomethine ylides with chiral furanones.

Meyers *et al.* have studied the addition of azomethine ylides **98** to chiral unsaturated bicyclic lactams **99**.⁷⁴⁻⁷⁷ The diastereoselectivities are dependent on the various substituents R^1 - R^4 ; for R^1 = Me, Ph, the major stereoisomer obtained is **100**, whereas for R^1 = H the epimer at C-8b is formed (Scheme 31).⁷⁷



Scheme 31: 1,3-DC of azomethine ylides with chiral bicyclic lactams

In addition, it was found that for R³ = H, the π -facial selectivity is insensitive to chiral substituents in the 1,3-dipole (R⁴ = chiral group), whereas when R³ is an electron-withdrawing substituents lower selectivities were observed. The 1,3-DC reaction of these azomethine ylides with chiral unsaturated bicyclic lactams was used for the synthesis of the (+)-conessine precursor (+)-benzohydrindan **101** (Figure 16).⁷⁶

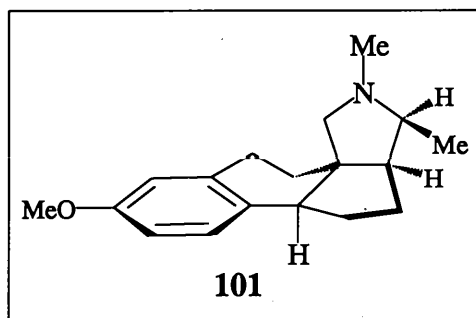
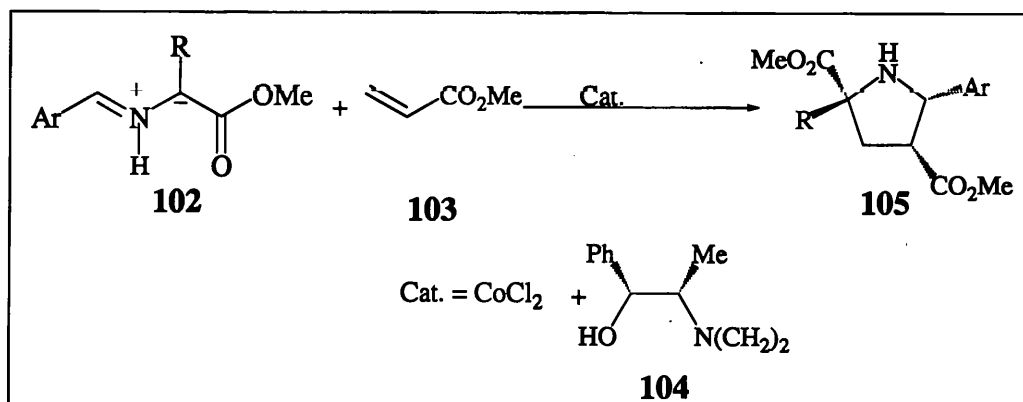


Figure 16: (+)-benzohydrindan

1.3.6 Chiral catalysis of 1,3-DC reactions

Grigg *et al.* have found that chiral Ag(I), Co(II) and Mn(II) complexes are excellent catalysts for the 1,3-DC reaction of azomethine ylides derived from arylidene imines of glycine.^{78,79} Reaction of azomethine ylides **102** with methyl acrylate **103** in the presence of

a stoichiometric amount of Co(II) and the chiral ephedrine ligand **104** gave the best yield (84%) and *ee* (96%) of the 1,3-DC reaction product **105** (Scheme 32).



Scheme 32: 1,3-DC reaction catalysed by Co (II) complexes

The presence of Ag(I) salts in combination with chiral ligands can catalyse similar 1,3-DC with *ee* of about 70%.⁶⁵ The postulated working model for the asymmetric induction is based on **106** (Figure 17).⁶⁵

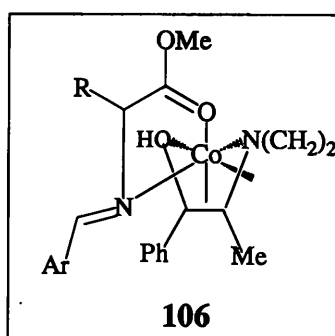
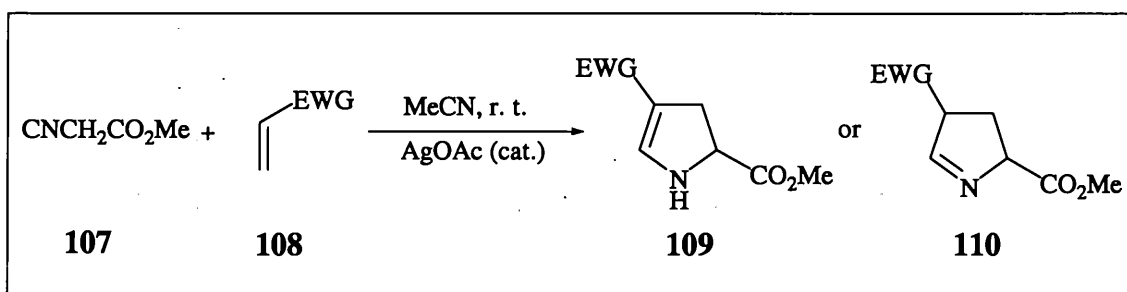


Figure 17: Postulated asymmetric induction model for formation of **105**.

The *cis* arrangement of the methyl group and phenyl group of the ligand result in a pseudoequatorial conformation of the phenyl group and provides an effective blockage of one of the faces of the dipole.

Silver acetate is also an efficient catalyst for the cycloaddition of the azomethine ylide precursor methyl isocyanoacetate **107** with a range of olefins bearing conjugated activating groups **108**. The reactions proceed smoothly at ambient temperature with 0.2–2 mol % of the catalyst to give, depending on the nature of the olefin used, either pyrroline **109** or pyrroline **110** in good yields (Scheme 33).⁷⁹



Scheme 33: Silver acetate as catalyst in 1,3-DC reactions of azomethine ylides

Throughout this introductory Chapter we have endeavoured to provide the reader with the relevant background information on 1,3-DC reactions, as well as on the generation of azomethine ylides as specific 1,3-dipole components of these reactions. The synthetic utility of the latter in 1,3-DC chemistry has also been outlined.

Our project concerns the synthesis of novel imidazolinium ylides as azomethine ylides and their subsequent 1,3-DC chemistry with a range of dipolarophiles in both an *inter*- and *intramolecular* sense. The chemistry and results involved in this project follow.

Chapter 2

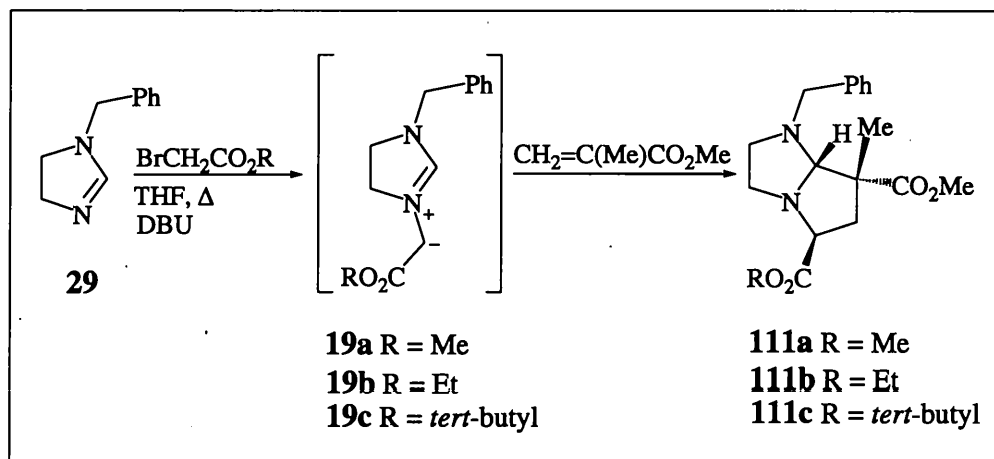
Results and Discussion

2.1 Intermolecular approach

This section describes approaches to the synthesis of dihydroimidazoles substituted with a heteroatom at C-2, their conversion into azomethine ylides, and our attempts to perform 1,3-DC reactions between the latter and a variety of dipolarophiles.

2.1.1 C-2 substituted dihydroimidazoles and imidazolinium ylides in 1,3-dipolar cycloaddition reactions

Previous researchers in our group have developed methodologies whereby azomethine ylides such as **19** are generated from the N-alkylation of 4,5-dihydroimidazoles **29** and subsequent deprotonation of the salts so-formed. These ylides undergo 1,3-DC reactions with a wide variety of dipolarophiles, to afford functionalised pyrroloimidazoles, for example **111** (Scheme 34), and hence pyrrolidines and pyrroles.^{41,80,42}



Scheme 34

In these reactions *endo* adducts predominate and only traces of the *exo* diastereoisomers are formed. The dipole appears to have an *anti* geometry in which the H atom is on the opposite face of the imine functionality of the dipole. The proposed transition state (Figure 18) is consistent with other results involving azomethine ylides generated from iminium salts.⁸¹⁻⁸³

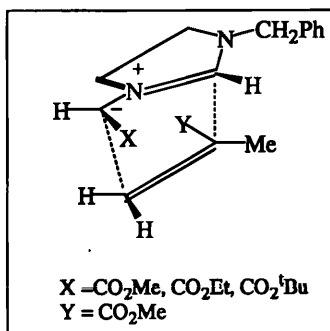


Figure 18: Proposed transition state for 1,3-DC reaction described in Scheme 34

The relative stereochemistry of the cycloadducts was secured by ^1H nuclear Overhauser enhancement (n.O.e.) spectroscopy and by X-ray crystallographic analysis in the chiral series (see later). For adduct **111b**, enhancement of the signal for the C-7a bridgehead proton on irradiation of the C-7 methyl group protons confirms that these two substituents are on the same face of the molecule, consistent with an *endo* approach of the dipolarophile to the azomethine ylide dipole (Figure 19).

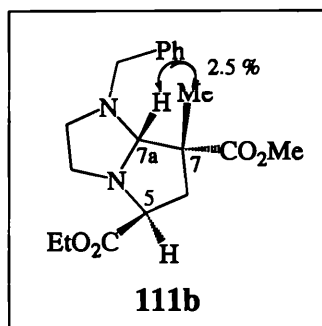
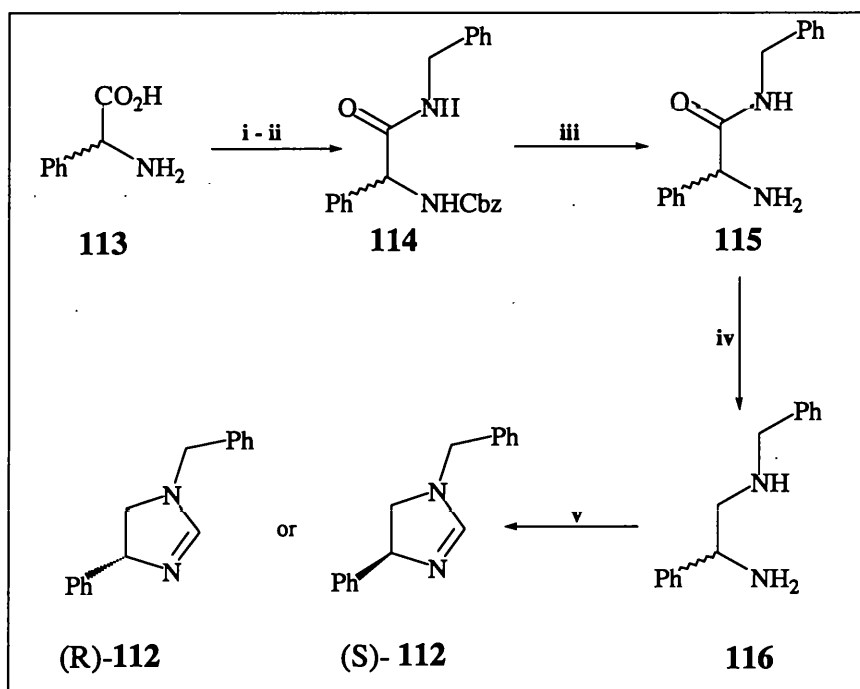


Figure 19: Relative stereochemistry of adduct **111b** according to n.O.e. studies

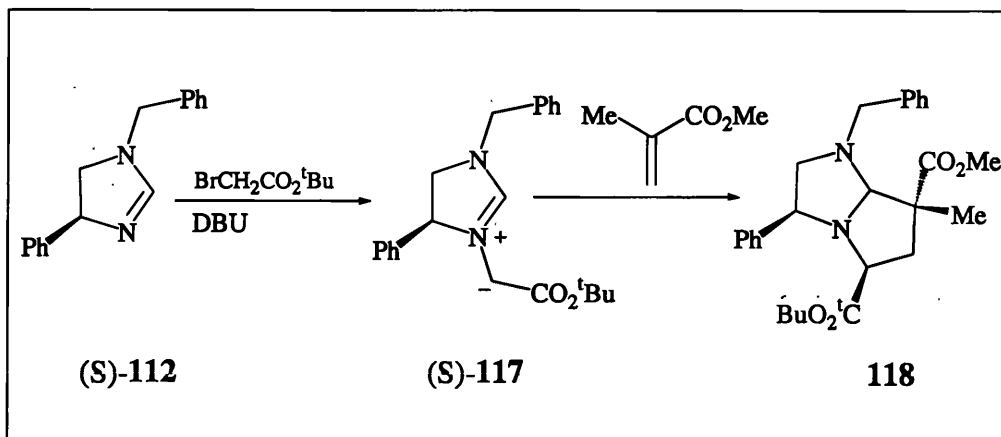
The observed regiochemistry of cycloaddition is as expected for the addition of an electron-deficient dipolarophile to a stabilised azomethine ylide (*i.e.* one carrying an electron-withdrawing group attached to the formally negatively charged end of the dipole) with an electron-deficient dipolarophile; orbital control involves HOMO-dipole / LUMO-dipolarophile interactions. This work was extended to optically active azomethine ylides generated from the homochiral dihydroimidazole **112** that can be synthesised from the commercially available optically active amino acid phenylglycine **113** (Scheme 35).⁸⁴



Reagents: **i**, $\text{PhCH}_2\text{OCOC}\text{Cl}$, aq. NaOH ; **ii**, $\text{N-methylmorpholine}$, EtOCOCCl , BnNH_2 ; **iii**, H_2 , Pd-C ;
iv, $\text{BH}_3\cdot\text{THF}$; **v**, $\text{HC}(\text{OEt})_3$, $p\text{-TsOH}$

Scheme 35

The chiral azomethine ylides **117** were found to exhibit complete facial discrimination in their 1,3-DC reactions with a variety of dipolarophiles, affording, for example, the pyrroloimidazole **118** with methyl methacrylate (Scheme 37).⁸⁵



Scheme 37

Again, stereochemistry was confirmed by n.O.e. and X-ray studies. The stereochemical outcome of the cycloaddition is consistent both with an *endo* approach of the dipole and the dipolarophile and with the dipole having the *anti* geometry; facial selectivity is provided by the 4-phenyl substituent in the dipole. This is summarised in Figure 20.

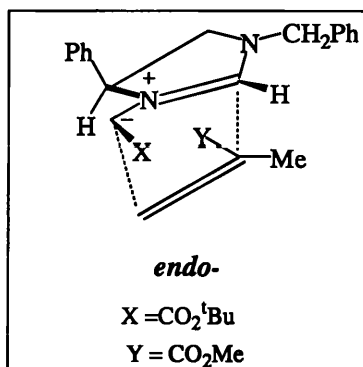
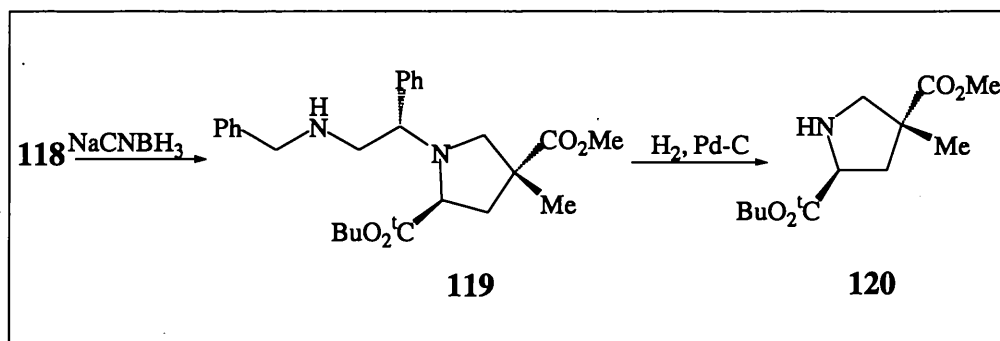


Figure 20: *Endo* transition state for **118**

The cycloadduct **118** could be elaborated by a simple yet highly efficient two-step template removal protocol to yield optically active substituted pyrrolidines **120** (Scheme 38).⁸⁶



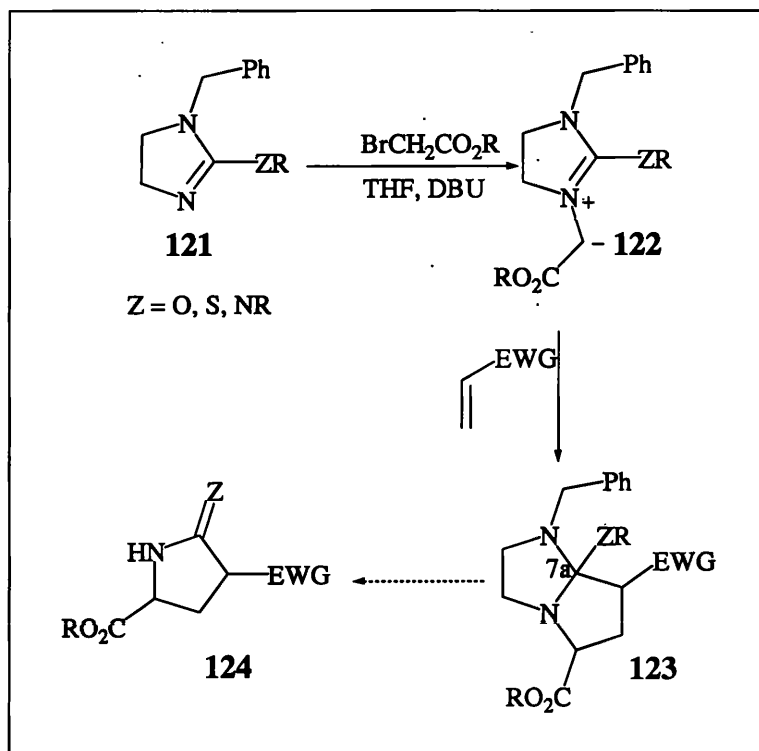
Scheme 38

In summary, cycloaddition using azomethine ylides generated from achiral and chiral dihydroimidazoles constitutes a powerful synthetic tool that affords access to polyfunctionalised pyrroloimidazole and pyrrolidine systems.

2.1.2 Strategy

Bearing in mind the azomethine ylide methodology described above, we proposed to prepare dihydroimidazoles substituted at C-2 with a heteroatom (O, S and N) that would constitute the precursors for a new generation of azomethine ylides. We anticipated that 1,3-DC reaction conditions involving such ylides **122** would afford hexahydropyrrolo[1,2-*a*]imidazoles **123** possessing additional heteroatom functionality at the bridgehead carbon (C-7a) (Scheme 39). Our strategy was to introduce sulfur functionality (SR) to the C-2 position of dihydroimidazole **29**.⁸⁷ Dihydroimidazoles substituted with sulfur at C-2 would have a two-fold significance. In addition to acting as precursors for new sulfur-containing

azomethine ylides such as **122**, they could be intermediates from which to synthesise the dihydroimidazoles substituted with O- and N- at C-2. This latter property arises from the inherent leaving group ability of the SR species; *i.e.* treatment of dihydroimidazoles carrying SPh or SBu at C-2 with an oxygen or nitrogen nucleophile, *e.g.* an alkoxides or a secondary amine, would afford the desired O- and N- substituted dihydroimidazoles **121** *via* substitution and concomitant loss of the thiol or thiolate.



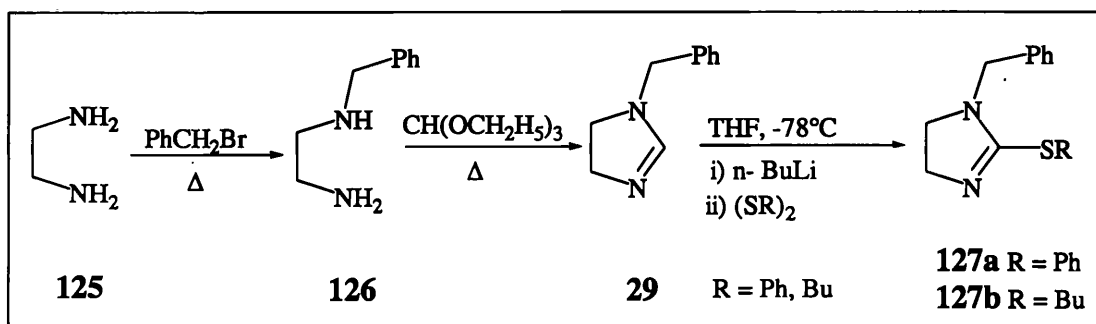
Scheme 39

The C-2 substituted dihydroimidazoles **121** would be *N*-alkylated using an activated haloalkane such as methyl bromoacetate to afford the azomethine ylides **122** after deprotonation. Application of the standard 1,3-DC reaction conditions, *i.e.* treatment of **122** with excess dipolarophile followed by addition of DBU, would then follow. Our expectation was that removal of the dihydroimidazole template would furnish the

pyrrolidones **124**. We proposed to explore the methodology in the achiral series shown in Scheme 39 before applying it to chiral systems.

2.1.3 Synthesis of dihydroimidazoles substituted at C-2 with heteroatoms and attempted 1,3-dipolar cycloaddition reactions

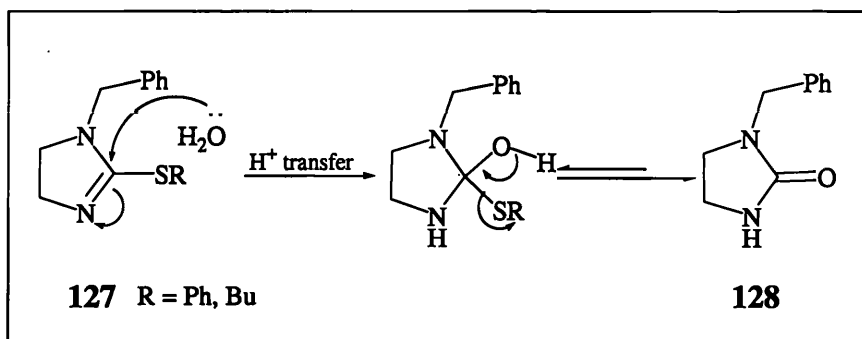
We took as the starting point the synthesis of sulfur-substituted dihydroimidazoles since previous researchers in our group had reported a protocol for the introduction of the SPh group onto the C-2 position of dihydroimidazole **29**.⁸⁷ Thus, we treated an anhydrous THF solution of the dihydroimidazole **29**, synthesised from commercial 1,2-diaminoethane **125** by N-alkylation with benzyl chloride to afford **126** followed by ring closure using triethyl orthoformate,⁴² with n-butyllithium at -78°C under a nitrogen atmosphere to obtain the C-2 deprotonated dihydroimidazole, which was then treated with diphenyldisulfide to afford the phenylthio-substituted dihydroimidazole **127a** in 36 % yield (Scheme 40).



Scheme 40

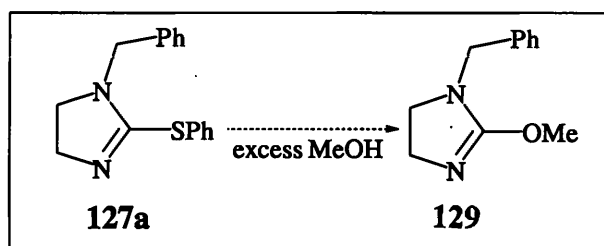
Although this methodology allowed us to access the butylthio analogue **127b** (using dibutyldisulfide as electrophile) in 21% yield, the yield for both reactions was low. Indeed, in both cases, the major product (40%) of the reaction was 1-benzyl-4,5-dihydroimidazol-

2-one **128**. We suspect this arises from the presence of adventitious water during work-up; a route involving hydrolysis is shown in Scheme 41.



Scheme 41

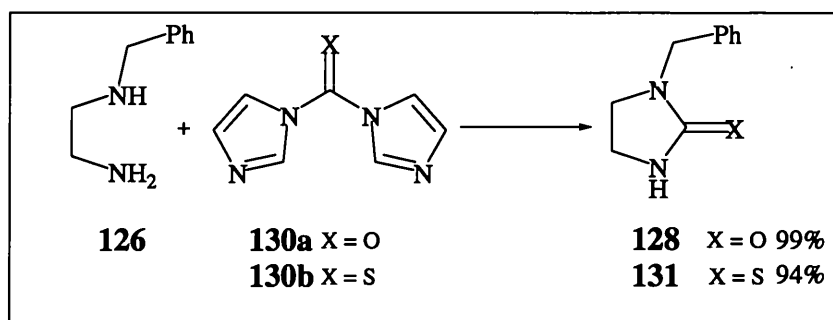
Despite these unsatisfactory results, we decided to investigate whether these sulfur-substituted dihydroimidazoles could be used successfully as precursors to their oxygen counterparts. We envisaged using a fairly straightforward methodology, *i.e.* treatment of the sulfur substituted dihydroimidazole **127a** with an appropriate alcohol (Scheme 42).



Scheme 42

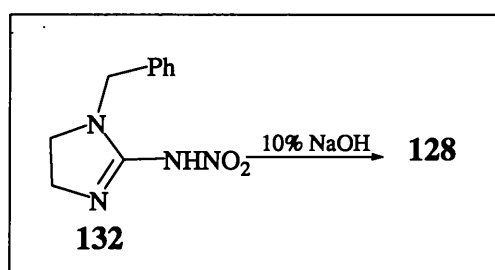
However, this approach proved unsuccessful despite using reflux conditions and the use of alkoxide nucleophiles (*e.g.* $\text{Na}^+ \text{OEt}^-$; 2.5 equiv.) in ethanol as solvent. We therefore adopted a different approach based on the parent tetrahydroimidazol-2-one **128** and thione **131** (Scheme 43). These were available in high yield (>90%) by treating a THF solution of

N-benzyl-1,2-diaminoethane **126** with a THF solution of either commercial 1,1'-carbonyldiimidazole **130a** or 1,1'-thiocarbonyldiimidazole **130b** (Scheme 43).



Scheme 43

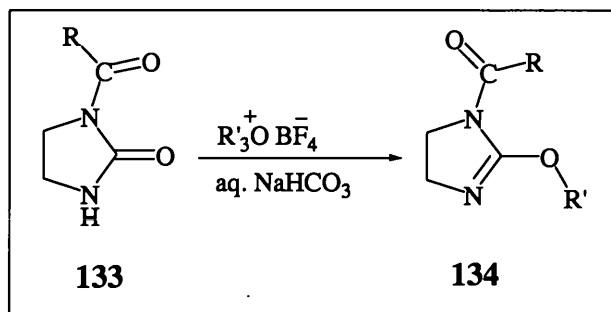
To the best of our knowledge, for cyclic urea **128** there have been only two other reported syntheses. The first, reported by McKay and co-workers,⁹⁰ involved hydrolysis of 1-benzyl-2-nitroamino-2-imidazoline **132** using 10% aqueous sodium hydroxide to afford **128** in 91% yield (Scheme 44).



Scheme 44

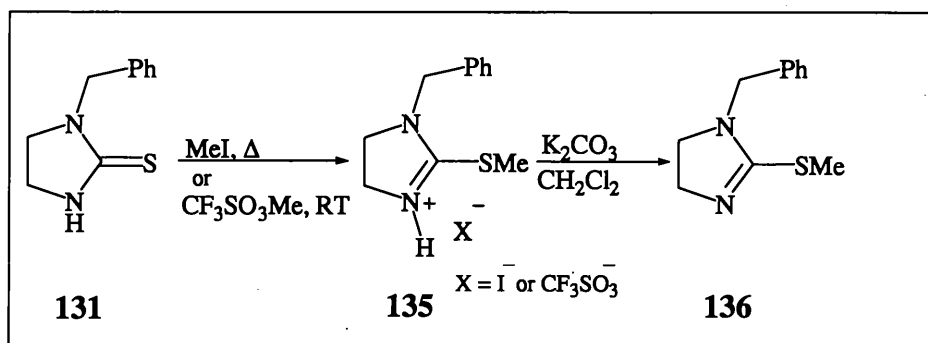
The second, published by previous researchers in our group,⁸⁷ involved isolation of **128** in 25% as a hydrolysis by-product from the synthesis of 1-benzyl-2-phenylthio-2-imidazoline **127a** (see Scheme 41), as we also reported above.

With the heteroatom-substituted dihydroimidazoles **128** and **131** to hand, we attempted their alkylation. To introduce alkyl functionality at the oxygen atom of the tetrahydroimidazol-2-one **128**, we chose to follow methodology developed by Kohn and co-workers,⁸⁹ where O-alkyl-N-acylimidazolines **134** were prepared by reaction of trialkyloxonium tetrafluoroborates (Meerwein salts)⁹⁰ with the N-acylimidazolidone **133** (Scheme 45).



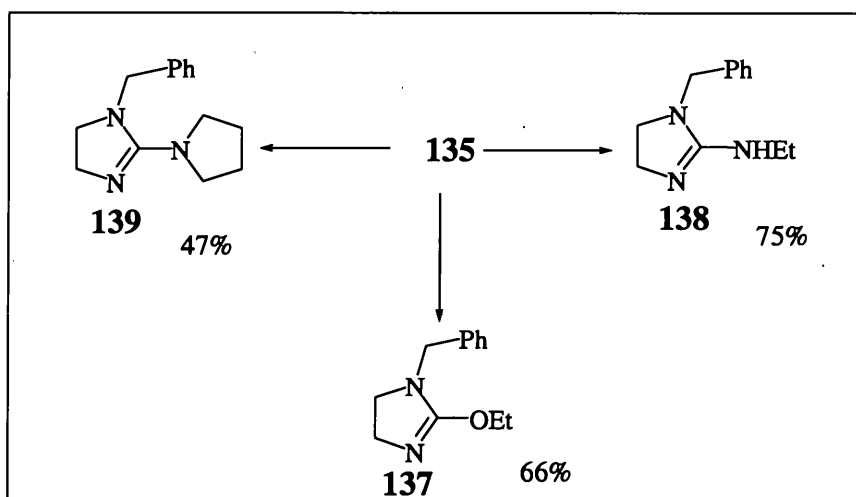
Scheme 45

In our hands this methodology failed to produce the desired O-alkylated dihydroimidazole, the starting materials invariably being recovered in quantitative yield. The use of other alkylating agents such as methyl trifluoromethanesulfonate, or an increase in the equivalents of alkylating agent used, also proved unsuccessful. Indeed, reaction of tetrahydroimidazol-2-one **128** with excess methyl trifluoromethanesulfonate for 72h at RT afforded only traces of the desired O-alkylated product according to spectroscopic analysis. In contrast, introduction of an alkyl functionality into sulfur-substituted dihydroimidazole **131** proved facile. Treatment of **131** with either excess iodomethane or methyl trifluoromethanesulfonate afforded the methylthioimidazolinium salt **135** which, upon treatment with excess K_2CO_3 gave the desired free base 1-benzyl-2-methylthio-4,5-dihydroimidazole **136** in 86% yield (Scheme 46).



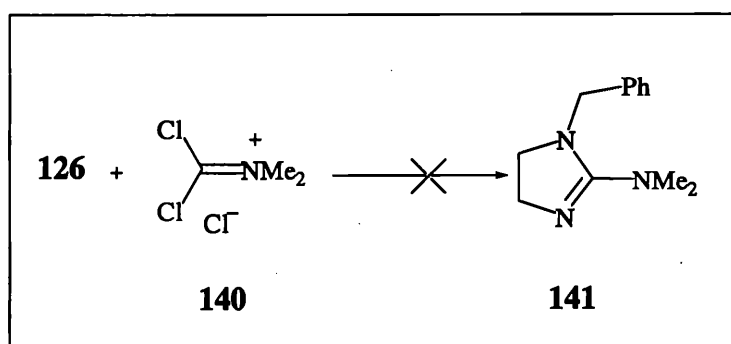
Scheme 46

In fact, the methylthioimidazolium salt **135** proved central to the synthesis of several related derivatives. For example, reaction of the salt **135** with a freshly prepared solution of NaOEt in ethanol under reflux for 24 h afforded upon work-up the desired 1-benzyl-2-ethoxy-4,5-dihydroimidazole **137** in 66% yield (Scheme 47). Further, the salt **135** could be used to synthesise N-substituted derivatives **138** and **139** by reaction with either a 2M THF solution of EtNH₂ under reflux for 20 h to afford 1-benzyl-2-ethylamino-4,5-dihydroimidazole **138** in 75% yield or with pyrrolidine under reflux for 20 h to afford 1-benzyl-2-(pyrrolidin-1-yl)-4,5-dihydroimidazole **139** in 47% yield (Scheme 47).



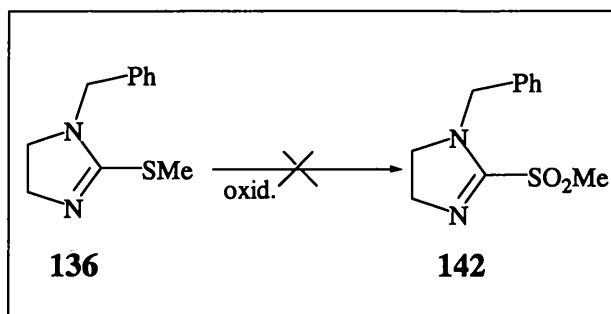
Scheme 47

Unfortunately, the use of the bulkier primary amine *tert*-butylamine and the aromatic amine aniline failed to produce the corresponding nitrogen-substituted dihydroimidazoles; invariably starting material was recovered quantitatively. We also attempted the synthesis of a nitrogen-substituted dihydroimidazole using a similar approach to the one developed for the oxygen and sulfur species depicted in Scheme 43. We anticipated that coupling the phosgene iminium chloride **140** with 1-benzyl-1,2-diaminoethane **126** would lead to the 1-benzyl-2-dimethylamino-4,5-dihydroimidazole **141**. This approach proved unsuccessful with only starting material **126** being recovered (Scheme 48).



Scheme 48

Attempts to oxidise 1-benzyl-2-methylthio-4,5-dihydroimidazole **136** to its sulfone derivative **142** (Scheme 49) failed in our hands. Oxidising agents such as oxone® and *m*-chloroperbenzoic acid (*m*-CPBA) were used, as well as different reaction conditions (temperature, solvents, increase of equivalents of oxidising agent), but in all cases we did not observe the formation of a new product by thin layer chromatography.



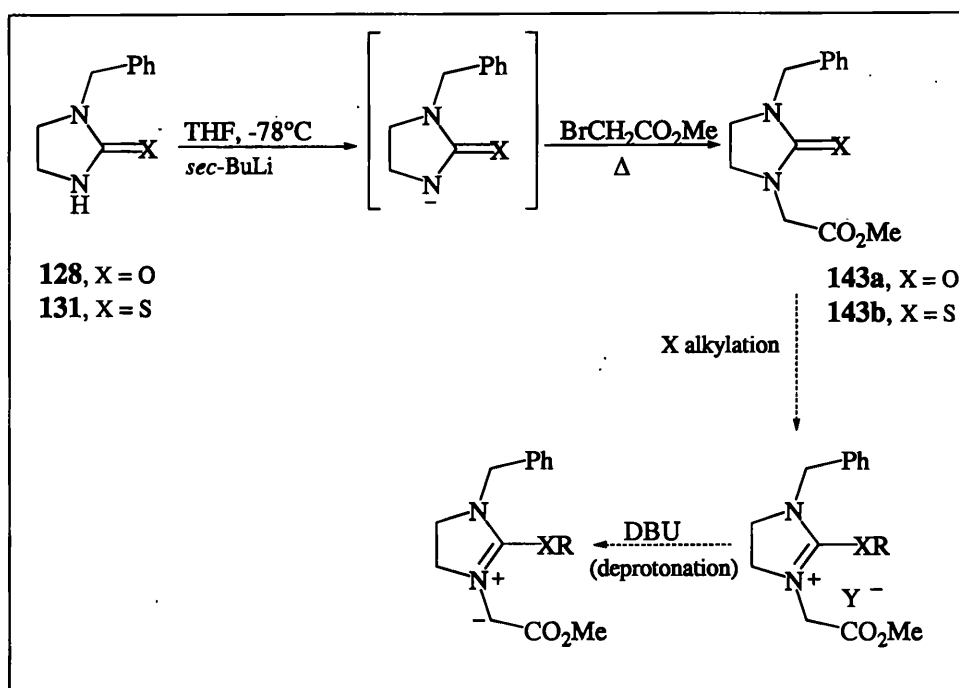
Scheme 49

However, since we had at this stage achieved the synthesis of heteroatom substituted dihydroimidazoles such as **136**, **137**, **138** and **139**, we proceed to investigate the N-alkylation of these substrates, as would be required *en route* to azomethine ylides.

We used 1-benzyl-2-methylthio-4,5-dihydroimidazole **136** as the model substrate and thus reacted a solution of the latter in THF with methyl bromoacetate under refluxing conditions for 5 h. After the removal of solvent under reduced pressure the crude residue was analysed by ^1H NMR spectroscopy. Unexpectedly, the crude residue was characterised as the starting material **136**, implying no reaction with the alkylating agent. In order to tackle this low reactivity,⁹¹ we decided to use more reactive alkylating agents such as iodoacetonitrile as well as those bearing mesylate leaving groups such as ethyl methylsulfonyloxyacetate, synthesised from ethyl glycolate with methanesulfonyl chloride. However, none of these proved successful and invariably the substrate **136** was the only isolated material from these reactions that could be characterised. Applying the same methodology to the oxygen and nitrogen substituted dihydroimidazole species **137** and **138**, respectively, produced identical results.

In the light of these results, we modified our strategy by reversing the elaboration of substituents and attempting first the synthesis of tetrahydroimidazol-2-ones and -2-thiones already bearing an *N*-methoxycarbonylmethyl substituent, *e.g.* **143a** and **143b**, respectively

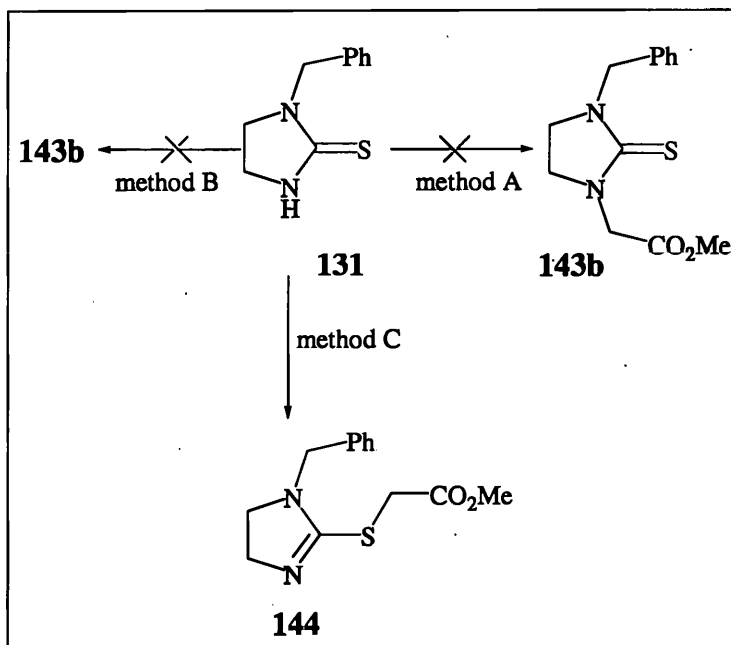
(Scheme 50). We envisaged that subsequent alkylation at the X heteroatom would generate imidazolium salts from which the desired ylides could be formed by deprotonation. Thus, 1-benzyltetrahydroimidazol-2-one **128** was reacted in anhydrous THF under nitrogen at -78°C with *sec*-BuLi to form the corresponding anion. The resulting solution was treated with methyl bromoacetate and subsequently heated at reflux for 24 h to afford the desired 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one **143a** in 41% (Scheme 50). Attempts to improve the yield by the use of other bases such as *n*-BuLi, LDA, NaH and *tert*-butyllithium proved unsuccessful, with the highest yield of these being for *tert*-butyllithium (15%). Thus, *sec*-BuLi became the base of choice for the reaction.



Scheme 50

Unexpectedly, this methodology failed to produce the desired results when applied to 1-benzyltetrahydroimidazol-2-thione **131**. When either *sec*-BuLi or NaH were employed as the base, starting material was recovered in virtually quantitative yield (Scheme 51, method A). We also envisaged that the use of the Mitsunobu reaction would generate the

desired 1-benzyl-3-methoxycarbonylmethyl-4,5-dihydroimidazol-2-thione **143b**. Thus tetrahydroimidazole **131**, triphenylphosphine and ethyl glycolate were dissolved in dioxane, before diethyl azodicarboxylate (DEAD) was added (Scheme 51, method B). After 8 h work-up afforded unreacted starting material **131** (contaminated with traces of triphenylphosphine) in approximately 80%, and triphenylphosphine itself. Perhaps naively, we also attempted the synthesis of **143b** by simply treating a solution of **131** in dry THF with methyl bromoacetate and heating the resulting solution at reflux for 18 h. Silica gel column chromatography of the crude residue using a basic eluant afforded 1-benzyl-2-(methoxycarbonylmethylthio)-4,5-dihydroimidazole **144** in 87% yield (Scheme 51, method C). Since alkylation not surprisingly occurs at sulfur⁸⁹ rather than nitrogen, this approach to **143b** was unsuitable.



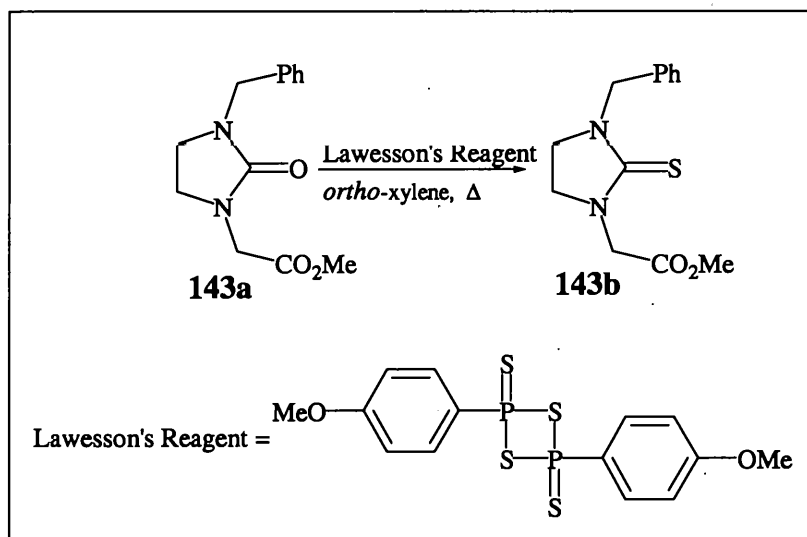
A: (i) THF, -78°C , *sec*-BuLi, (ii) $\text{BrCH}_2\text{CO}_2\text{Me}$, Δ , 18 h.

B: Ph_3P , $\text{HOCH}_2\text{CO}_2\text{Et}$, dioxane, DEAD.

C: THF, $\text{BrCH}_2\text{CO}_2\text{Me}$, Δ , 18 h.

Scheme 51

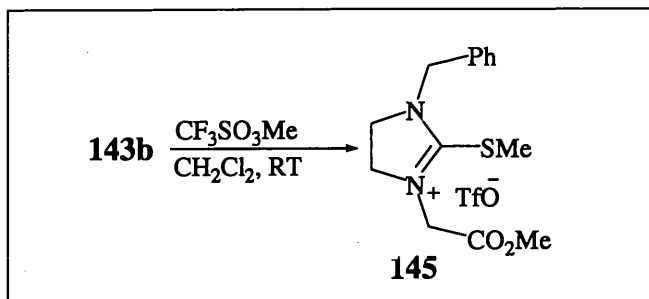
A successful synthesis of **143b** was finally developed by simple treatment of a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one **143a** in dry *ortho*-xylene under nitrogen with the thionating agent 2,4-bis-(4-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide⁹² (Lawesson's Reagent) and heating the resulting solution at reflux for 26 h. Column chromatography of the crude residue afforded **143b** in 66% (Scheme 52). The use of dry THF or anhydrous toluene instead of *ortho*-xylene as solvent resulted in decreased yields, 33% and 49%, respectively.



Scheme 52

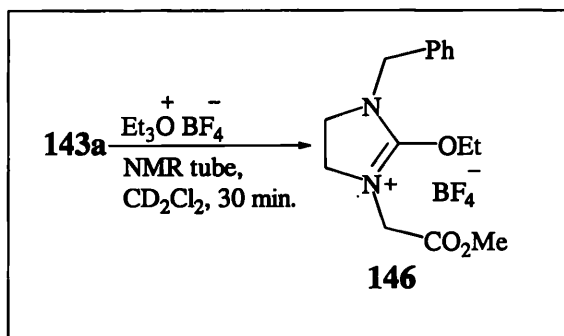
Having developed syntheses of **143a** and **143b**, we turned our attention to the introduction of a substituent onto the C-2 heteroatom in both of these molecules.

In the case of the sulfur analogue **143b**, methylation at sulfur was easily achieved by reaction with methyl trifluoromethanesulfonate in anhydrous dichloromethane under nitrogen for 1 h. This afforded 1-benzyl-3-methoxycarbonylmethyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate **145** in 97% yield (Scheme 53).



Scheme 53

Unsurprisingly, alkylation at the oxygen atom of 1-benzyl-3-methoxycarbonylmethyl tetrahydroimidazol-2-one **143a** proved to be a more challenging task due to the lower reactivity of the parent compound⁸⁹ and the known susceptibility of imidate salts to hydrolysis.⁹³ Under standard reactions conditions using an atmosphere of nitrogen we were unable to isolate the desired salt using the methylating agent methyl trifluoromethanesulfonate at RT even after increasing the amount of alkylating agent up to 10 equivalents. We decided to conduct a test reaction of the substrate **143a** with triethyloxonium tetrafluoroborate (1M solution in dichloromethane; 1.2 equiv.) as ethylating agent in a meticulously dried NMR sample tube, using deuterated dichloromethane as solvent and making the addition of the alkylating agent (1.2 equiv.) to **143a** *via* syringe inside a glove box. After 30 min the solution was analysed by ^1H NMR spectroscopy; no peaks corresponding to the starting material **143a** were observed and the spectrum clearly showed the formation of a new product that had peaks consistent with it being 1-benzyl-3-methoxycarbonylmethyl-2-ethoxy-4,5-dihydroimidazolium tetrafluoroborate **146** (Scheme 54).

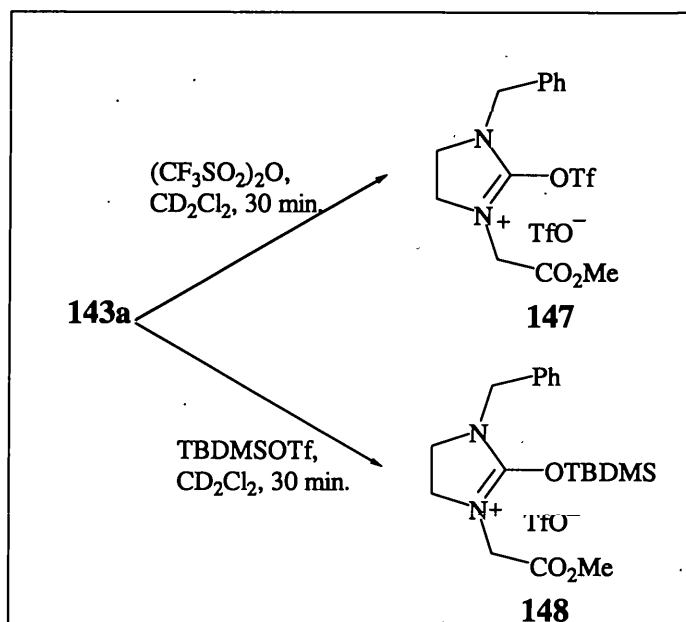


Scheme 54

The patterns of the signals corresponding to the newly formed salt **146** were analogous to those of the substrate **143a**, but there was a δ 0.5 downfield shift evident for each signal. This is consistent with the formation of the salt, the delocalised positive charge deshielding the protons in the molecule. In addition, the ethyl signals of the imidate ester salt **146** (triplet integrating to three protons at δ 1.60 and quartet integrating to two protons at δ 4.75) were observed, as were those of diethyl ether, the by-product of alkylation.

We also envisaged the use of other reagents that would introduce a substituent onto oxygen in **143a**. Thus, compound **143a** was treated with trifluoromethanesulfonic anhydride (Tf_2O) (1.2 equiv.) to afford the salt 1-benzyl-3-methoxycarbonylmethyl-2-trifluoromethanesulfonyloxy-4,5-dihydroimidazolium trifluoromethanesulfonate **147** in 80% yield according to NMR spectra (Scheme 55). Further, treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate afforded 1-benzyl-3-methoxycarbonylmethyl-2-*tert*-butyldimethylsilyloxy-4,5-dihydroimidazolium trifluoromethanesulfonate **148** in quantitative yield as seen in the NMR spectra (Scheme 55). Again, both salts **147** and **148** display 1H NMR spectroscopic evidence of downfield shifts of the relevant product peaks by δ 0.5 in comparison to the substrate **143a**. However, due to the hygroscopic nature of

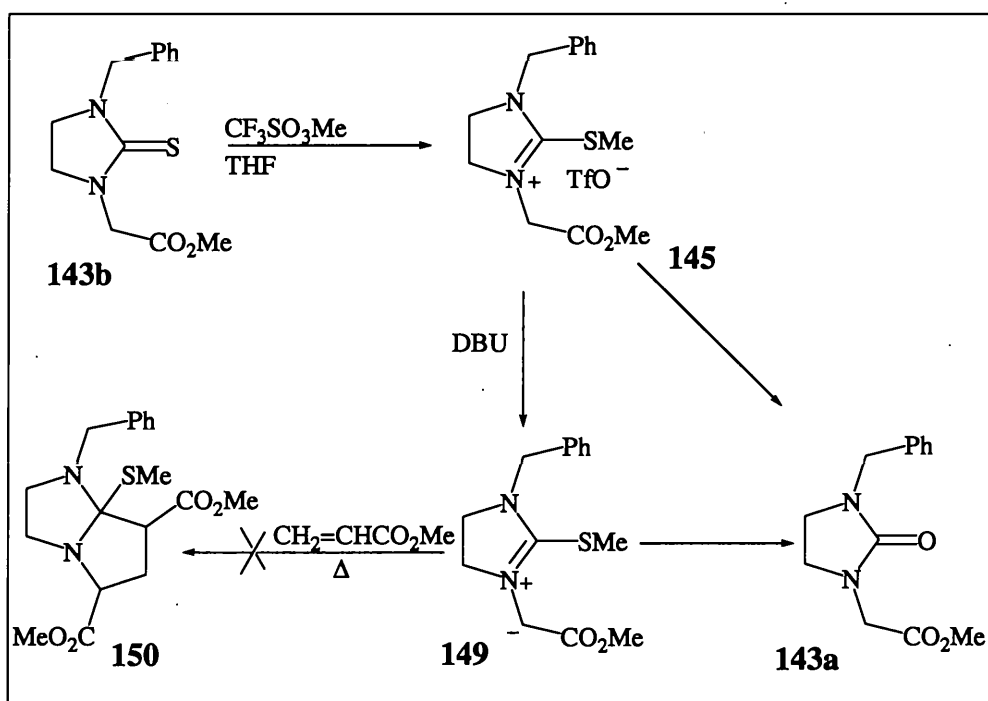
the salts **147** and **148**, prolonged ^1H NMR spectroscopic monitoring of these reactions revealed a gradual conversion of the salts with time to the starting material **143a**.



Scheme 55

We could now proceed to investigate a one-pot sequence whereby sulfur and oxygen derivatisation (alkylation, sulfonation or silylation) of the dihydroimidazoles **143a** and **143b** could be followed by deprotonation of the so-formed salts **145**, **146**, **147**, and **148**, respectively, as a way to attempt 1,3-DC reactions (see Scheme 56). Methyl trifluoromethanesulfonate (1.2 equiv.) was added to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione **143b** in anhydrous THF under nitrogen to afford the crude salt, 1-benzyl-3-methoxycarbonylmethyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate **145**. This was treated without isolation with an excess of the dipolarophile methyl acrylate (3 equiv.) and the solution brought to reflux before the dropwise addition of DBU (1.2 equiv.). However, the 1,3-DC reaction product expected from the trapping of with the azomethine ylide **149** with methyl acrylate,

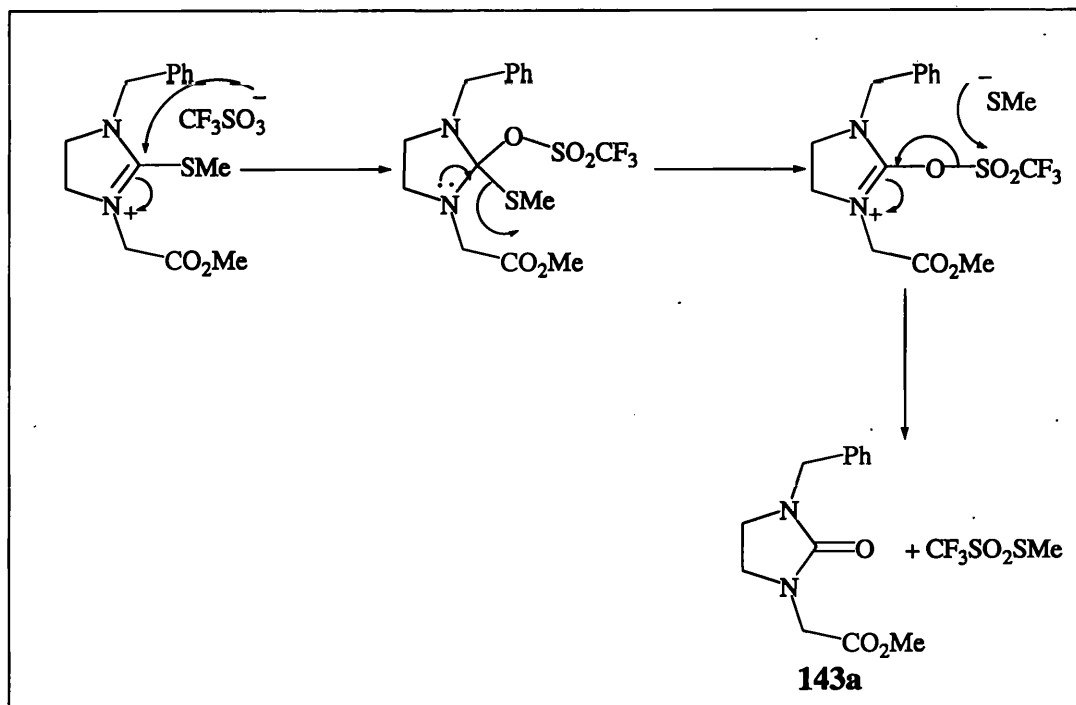
i.e. the hexahydropyrroloimidazole **150**, was not isolated (Scheme 56). Instead, the major material isolated after column chromatography of the crude residue was 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one **143a** in 87% yield. The other material isolated from this reaction was baseline material containing DBU residues, which could not be adequately characterised. The same reaction was also attempted using higher boiling solvents, such as toluene, and more polar solvents, such as dimethylsulfoxide; again, the major isolated material was 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one, **143a**, in yields varying from 80-85 %.



Scheme 56

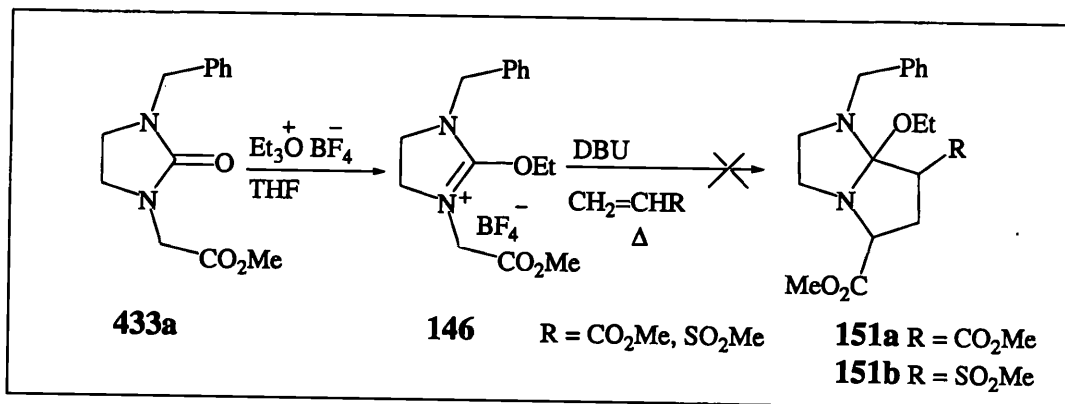
The formation of compound **143a** suggests that either the salt **145** or the azomethine ylide **149** was hydrolysed under the reaction conditions. Alternatively, though less likely, the salt **145** could afford the product **143a** by the route shown in Scheme 57, although the triflate

ion is not known to be particularly nucleophilic. Moreover, we did not obtain any evidence for the S-methyl trifluoromethanethiosulfonate by-product.



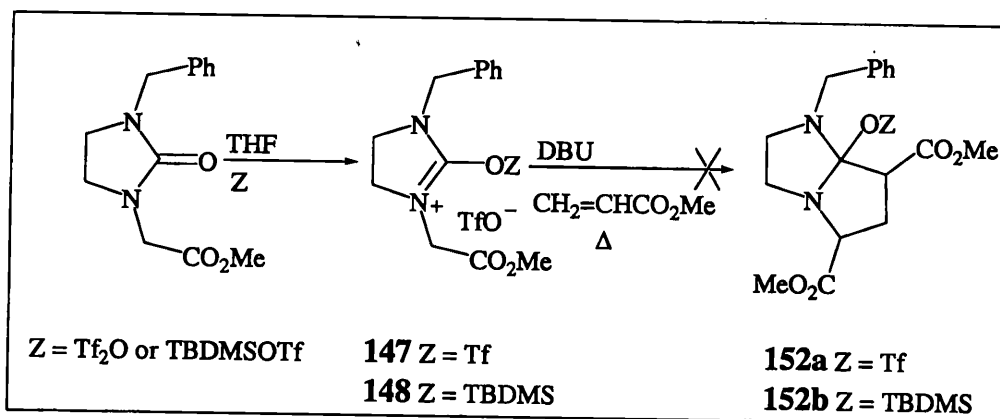
Scheme 57

Despite this lack of success with the sulfur analogue, we adopted a similar synthetic approach with the oxygen-substituted dihydroimidazole **143a**. Thus, O-alkylation of **143a** with triethyloxonium tetrafluoroborate (1.2 equiv.) followed by subjecting the so-formed salt **146** to DBU and methyl acrylate again resulted in isolation of the dihydroimidazol-2-one starting material **143a** rather than the hexahydropyrroloimidazole **151a** (Scheme 58). The use of more reactive dipolarophiles, such as methyl vinyl sulfone, afforded identical results and thus the hexahydropyrroloimidazole **151b** was not isolated.



Scheme 58

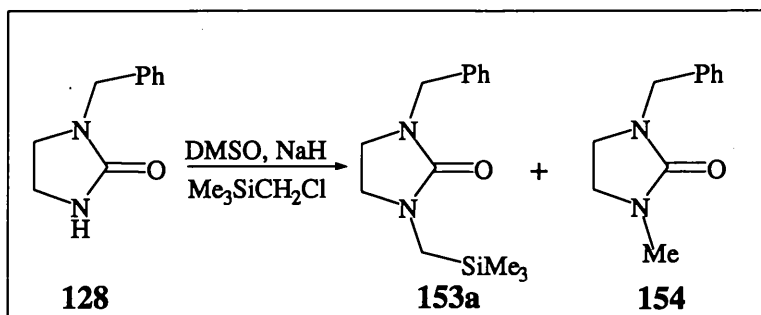
Similarly, the dihydroimidazole salts **147** and **148** were generated by treating 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one **143a** in anhydrous THF with Tf_2O or TBDMSOTf, respectively, and subsequently treated with excess methyl acrylate followed by DBU. However, neither reaction afforded the desired hexahydropyrroloimidazole **152a** or **152b**, respectively (Scheme 59). As before, the major isolated material was the 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one substrate **143a** in 85% and 89% yield, respectively. Use of toluene or acetonitrile as solvent afforded identical results.



Scheme 59

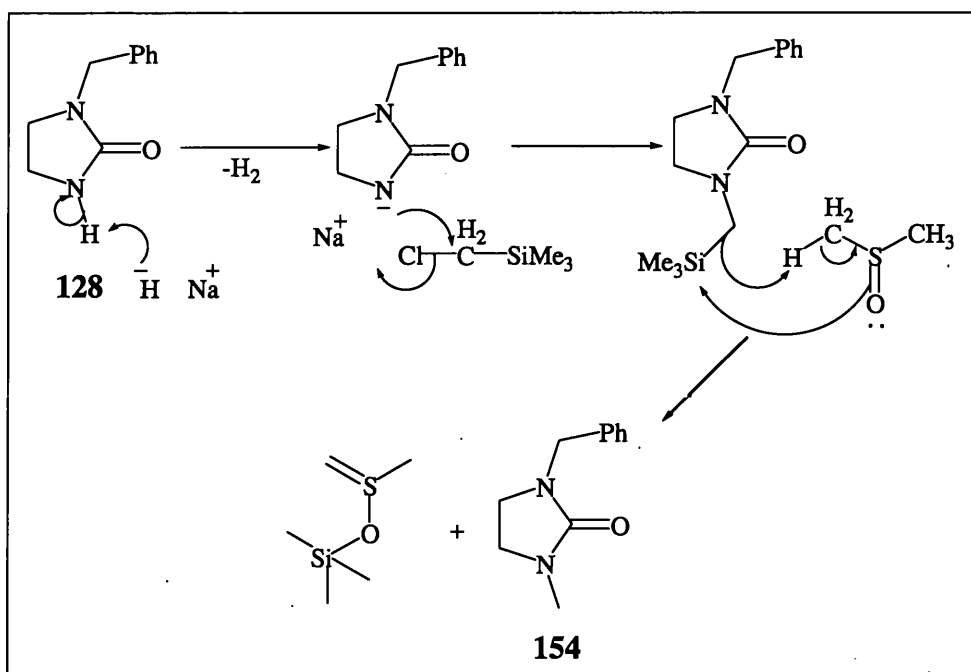
As an alternative approach to the formation of ylides from C-2 heteroatom-substituted dihydroimidazoles, we turned our attention to an approach based upon the desilylation methodology developed by Vedejs and co-workers for the synthesis of the pyrrolizidine alkaloid retronecine **56** (see Scheme 21).⁵⁵ This involved the fluoride ion-promoted desilylation of a silylalkyl substituent in an imidate salt **57** to afford the corresponding azomethine ylide, which subsequently underwent a 1,3-DC reaction with methyl acrylate to afford a bicyclic pyrrolizidine adduct.

To achieve this we needed first to introduce a silylmethyl substituent at the amide nitrogen of the tetrahydroimidazol-2-one **128** and the tetrahydroimidazol-2-thione **131**. Subsequent derivatisation of the oxygen and sulfur heteroatoms by the protocols described above would then afford the corresponding imidazolinium salts, which upon desilylation would generate the desired azomethine ylides. Silylmethylation of **128** was easily achieved through adaptation of the N-alkylation of **128** and **131** using methyl bromoacetate. Thus, reaction of 1-benzyltetrahydroimidazol-2-one **128** with NaH in anhydrous DMSO (use of THF as solvent led to lower yields) generated an imidazolone anion that was reacted with chloromethyltrimethylsilane to yield the desired 1-benzyl-3-trimethylsilylmethyl tetrahydroimidazol-2-one **153a** in 45% yield (Scheme 60). Also isolated was the 1-benzyl-3-methyl-tetrahydroimidazol-2-one **154** in 27% yield. The use of iodomethyltrimethyl silane as silylating agent afforded identical results. In contrast to the previous attempts to N-alkylate **128**, NaH afforded the best results in this reaction.



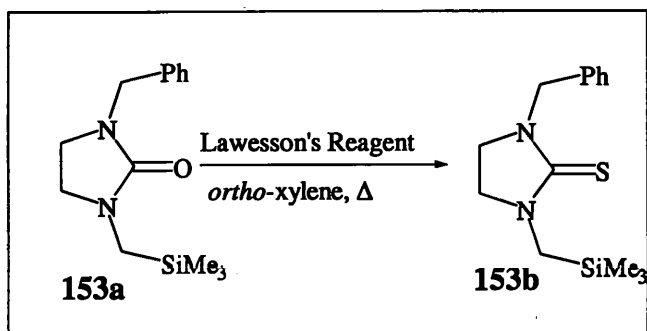
Scheme 60

The formation of 1-benzyl-3-methyl-tetrahydroimidazol-2-one **154** could be rationalised as shown in Scheme 61.



Scheme 61

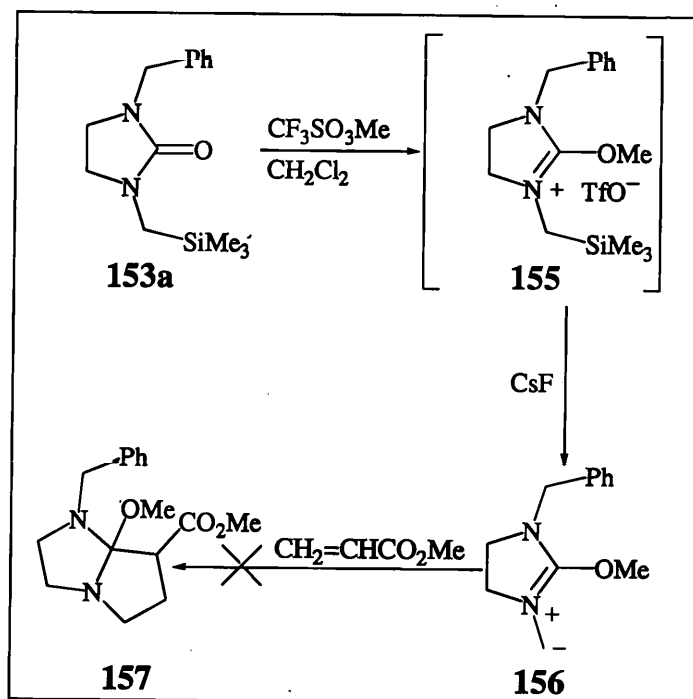
The sulfur analogue **153b** was obtained in 69% yield by treating **153a** in anhydrous *ortho*-xylene with Lawesson's Reagent (1 equiv.) under nitrogen (Scheme 62).



Scheme 62

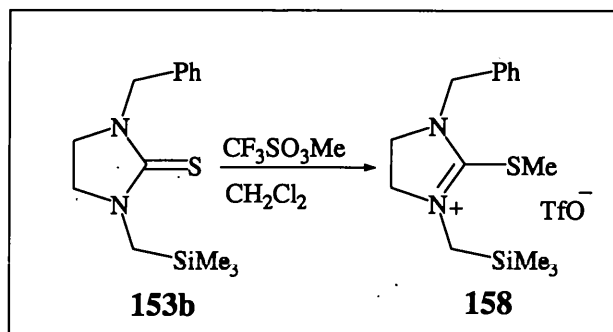
Not surprisingly, it proved difficult to introduce a substituent at the oxygen atom of **153a**. Reaction of **153a** with methyl trifluoromethanesulfonate and triethyloxonium tetrafluoroborate was monitored using ^1H NMR spectroscopy. The best results were obtained using methyl trifluoromethanesulfonate (5 equiv.), with O-methylation of **153a** proceeding to approximately 35% after 3 h (the conversion percentage was calculated from the integration of the methylene proton signal of **153a** in the ^1H NMR spectrum, relative to the methylene proton signal of the product **155**). Despite the low yield of the O-alkylation, we decided to attempt a one-pot reaction of **153a** towards the synthesis of hexahydropyrroloimidazoles **157** (Scheme 63). This involved initial O-alkylation to afford the salt **155**, followed by *in situ* fluoride-promoted desilylation using CsF and subsequent treatment of the so-formed ylide **156** with excess dipolarophile (Scheme 63). This required that all glassware was flame dried, and that solvents and caesium fluoride were meticulously dried prior to the reaction, since any adventitious water would compromise the progress of the reaction. Thus, 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one **153a** was treated with methyl trifluoromethanesulfonate (1.2 equiv.) in anhydrous dichloromethane at RT under nitrogen and the solution stirred for 3 h. The dichloromethane solvent was removed and replaced by 2-methoxyethyl ether, then methyl acrylate (3 equiv.) was added. The solution was transferred *via* syringe to a reaction flask

containing CsF (2.5 equiv.) under nitrogen. However, after subjection of the residue to silica gel column chromatography, the starting material **153a** was recovered in 89% yield (Scheme 63).



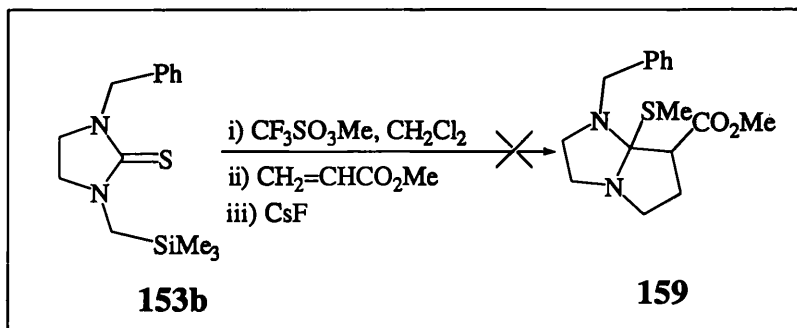
Scheme 63

Recovery of the starting material from this reaction could either be due to low conversion to the salt **155**, or to hydrolysis of **155** due to adventitious moisture. In either case, it was clear that fluoride ion-promoted desilylation had not taken place. Consequently, as we had the sulfur analogue **153b** to hand, and since we had developed a successful S-methylation of the sulfur atom in **153b** (Scheme 64), we decided to attempt the same one-pot methodology with the latter. Once again, the glassware was flame dried and all solvents and reagents were anhydrous.



Scheme 64

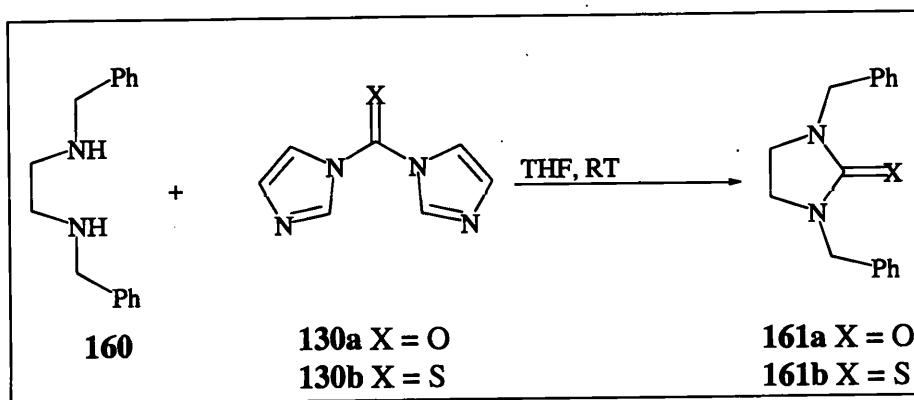
Thus, 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-thione **153b** was treated with methyl trifluoromethanesulfonate (1.2 equiv.) in anhydrous dichloromethane at RT under nitrogen for 3 h. The solvent was then removed and replaced by anhydrous diglyme, following which methyl acrylate (3 equiv.) was added. This solution was transferred *via* syringe to a reaction flask containing CsF (2.5 equiv.) under nitrogen and the subsequent mixture stirred at RT for 24 h. Unfortunately, purification of the crude residue by silica gel column chromatography did not afford the expected hexahydropyrroloimidazole **159**; instead, 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one **153a** was isolated in 37% yield together with recovered starting material 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-thione **153b** in 60% yield (Scheme 65). The former presumably arises from hydrolysis of the intermediate salt **158**, since **153b** is relatively stable to hydrolysis. These results imply that desilylation does not occur in these systems, so we abandoned this synthetic approach.



Scheme 65

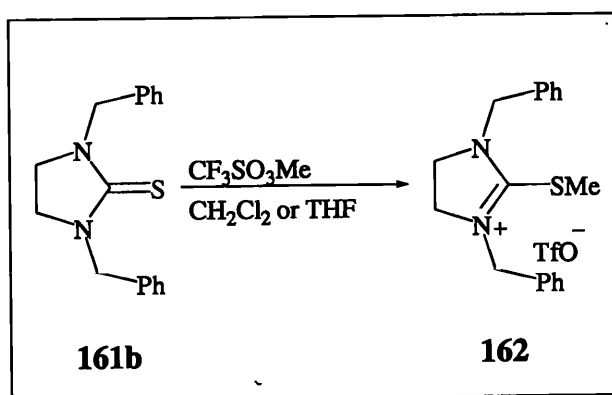
As a final approach to ylides from C-2 heteroatom substituted dihydroimidazoles we envisaged the use of the use of the dibenzylated species **161a** and **161b** (Scheme 66). We assumed that the heteroatom alkylation, silylation or sulfonation methodologies previously developed would be applicable to these dibenzylated species. Thus, the most relevant issue was whether or not the benzylic position of these species, after appropriate O- or S-substitution, would constitute the suitable deprotonation site essential for the formation of the desired azomethine ylides.

We were able to access 1,3-dibenzyltetrahydroimidazol-2-one **161a** in 97% yield, and 1,3-dibenzyltetrahydroimidazol-2-thione **161b** in 98% yield, by reacting a solution of commercial N, N'-dibenzyl-1,2-diaminoethane **160** in anhydrous THF with a THF solution of the appropriate coupling agent, 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole respectively, at RT for 18 h (Scheme 66).



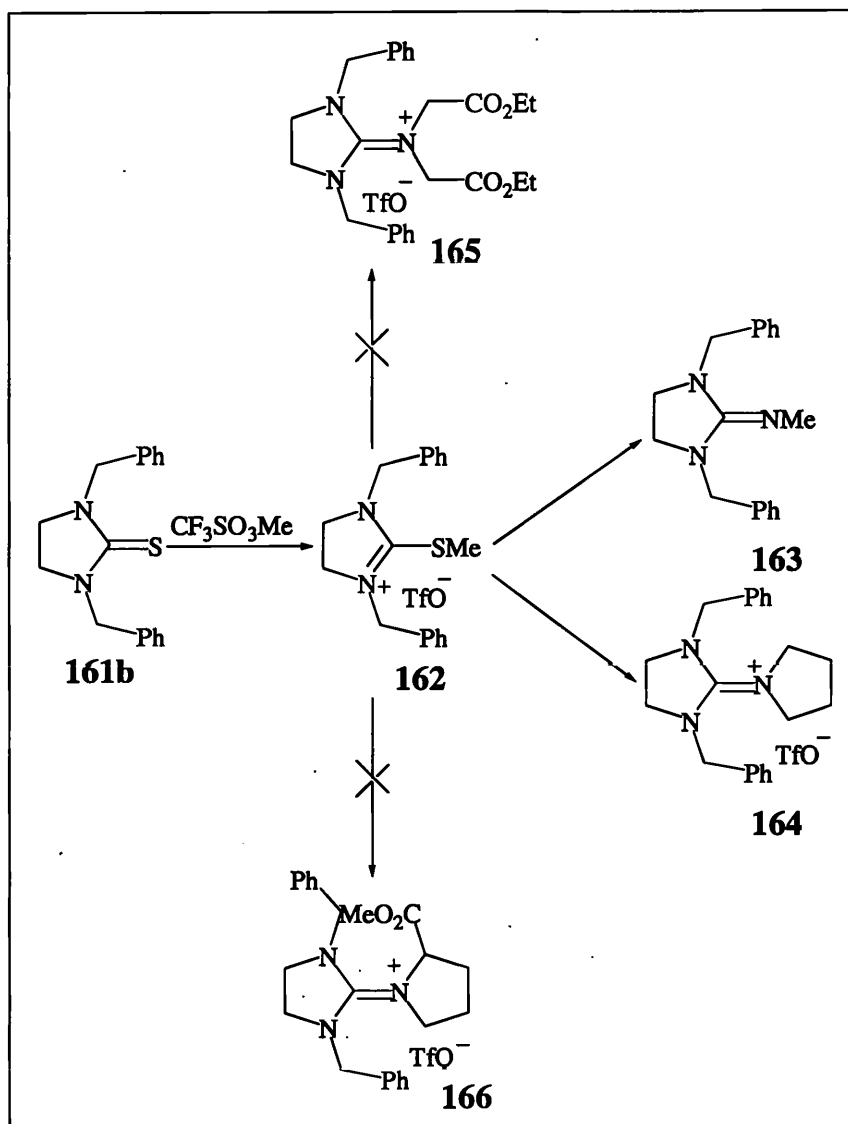
Scheme 66

We then investigated the S-alkylation of **161b** (Scheme 67), since the salts so-obtained are both potential azomethine ylide precursors and substrates for C-2 amination, the latter allowing us to access to 1,3-dibenzylated C-2 nitrogen-substituted dihydroimidazoles. As expected, quantitative methylation at sulfur in the dihydroimidazol-2-thione **161b** was achieved by treatment with methyl trifluoromethanesulfonate (1.2 equiv.) in anhydrous dichloromethane under nitrogen at RT (Scheme 67). The use of anhydrous THF as solvent produced identical results.



Scheme 67

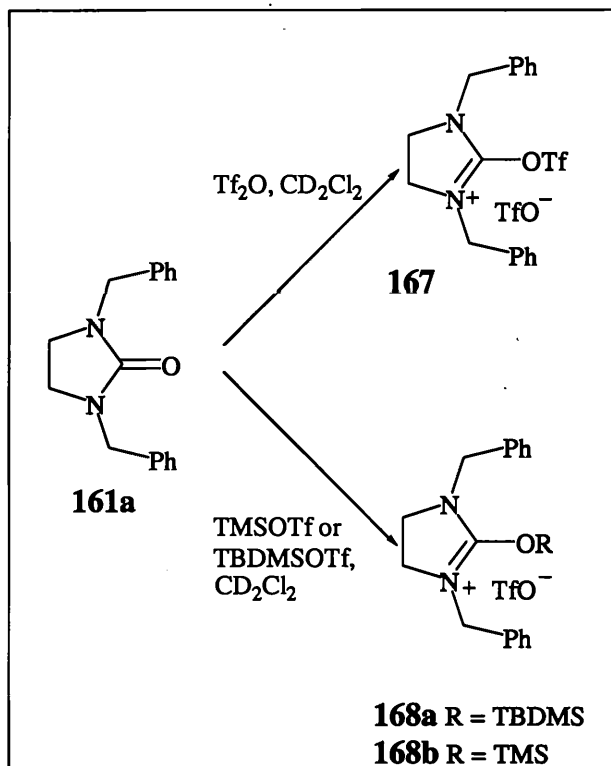
As planned, the dibenzylated salt **162** did afford access to dibenzylated C-2 nitrogen-substituted dihydroimidazoles. Thus, the 1,3-dibenzyltetrahydroimidazol-2-thione **161b** was methylated as described above, following which methylamine (2M solution in THF; 1.2 equiv.) was injected *via* syringe. After 18 h at reflux, the crude reaction residue was purified by silica gel column chromatography to give 1,3-dibenzyl-2-methyliminotetrahydroimidazole **163** in 40% yield (Scheme 68). Replacing methylamine by pyrrolidine and excluding the chromatographic purification step, we were also able to access the crude salt 1,3-dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolium trifluoromethanesulfonate **164** in 77% yield. ¹H NMR spectroscopic analysis of **164** showed the downfield shift of the corresponding proton signals of the amidine and pyrrolidine ring of **164** in comparison to the proton signals in the starting materials. As described above for similar systems such as **145**, this implies formation of the salt due to the deshielding effect caused by the delocalised positive charge. However, using either diethyl iminodiacetate or proline methyl ester as the nitrogen nucleophile proved unsuccessful. Monitoring these reactions in a sealed NMR tube at reflux using deuterated dichloromethane provided conclusive evidence that no reaction was taking place between these latter amines and the salt **162**. Replacement of deuterated dichloromethane by higher boiling solvents such as deuterated acetonitrile or toluene and using extended periods of reflux (72 h) or excess amine proved unfruitful (Scheme 68).



Scheme 68

Sulfonation or silylation at the oxygen atom of 1,3-dibenzyltetrahydroimidazol-2-one **161a** was achieved using Tf_2O and either trimethylsilyl trifluoromethanesulfonate or TBDMSOTf, respectively. Thus, addition of Tf_2O (1.2 equiv.) to a CD_2Cl_2 solution of 1,3-dibenzyltetrahydroimidazol-2-one **161a** afforded the O-triflated salt **167** in quantitative yield after 1 h, according to spectroscopic analysis. In the same manner, addition of either TMSOTf (1.2 equiv.) or TBDMSOTf (1.2 equiv.) to a CD_2Cl_2 solution of 1,3-dibenzyltetrahydroimidazol-2-one **161a** afforded the O-silylated salts **168a** and **168b**,

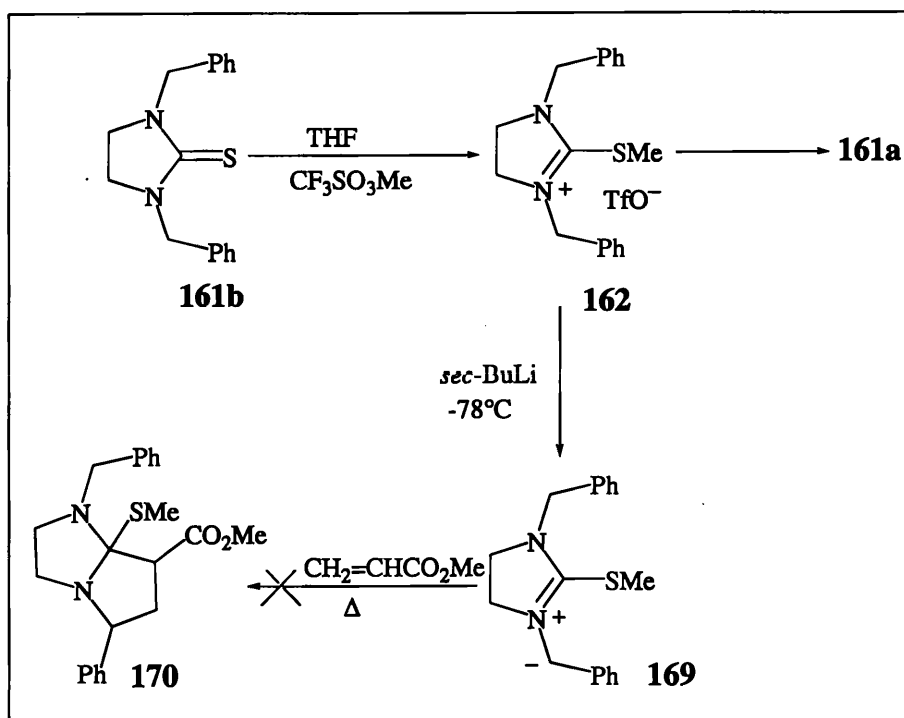
respectively, in quantitative yield as observed spectroscopically (Scheme 69). Again, the observed downfield shift of the amidine ring protons in the ^1H NMR spectrum, implying the formation of the corresponding salts, together with the absence of proton signals corresponding to either TMSOTf or TBDMSOTf starting materials, provided conclusive evidence.



Scheme 69

Having accessed to the S- and O- substituted salts **162** and **167/168**, respectively, we proceeded to investigate deprotonation at the benzylic site and subsequent 1,3-DC reaction with a suitable dipolarophile. We focused on the 1,3-dibenzyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate salt **162**, due to the simplicity of its synthesis and also to its stability towards hydrolysis. Thus, a solution of the salt **162** in anhydrous THF was cooled to -78°C , then treated with the base *sec*-BuLi (1.2 equiv.). We chose this base rather than DBU as the benzylic sites in **162** will be less acidic than the

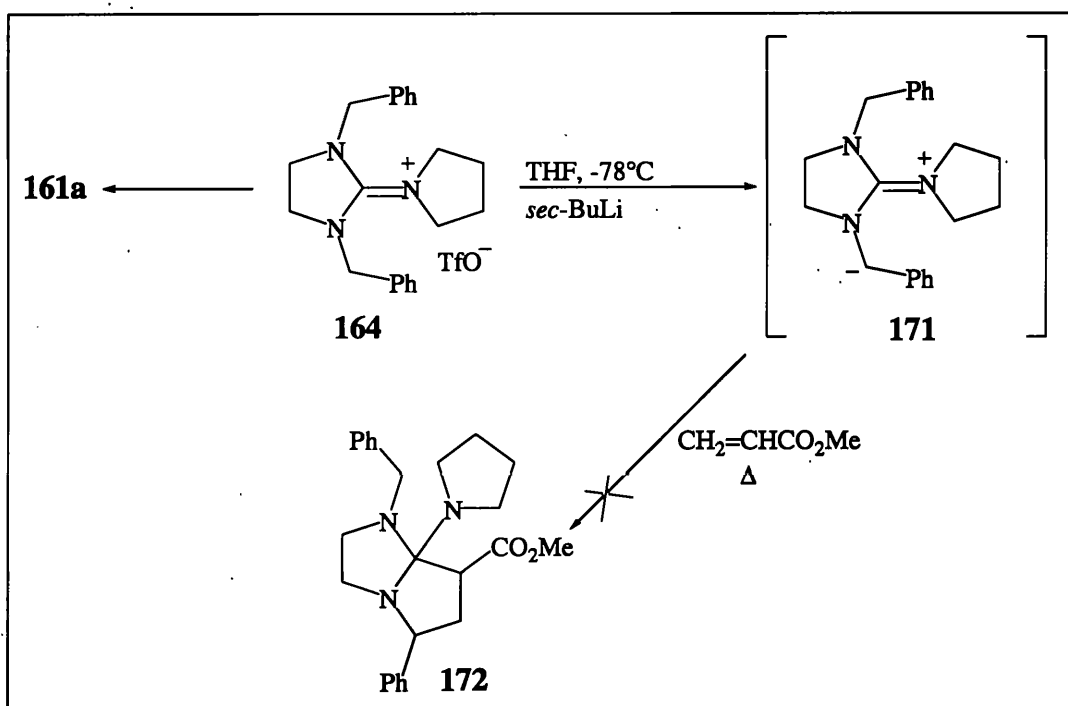
methylene site (α - to the ester group) in salts carrying an electron-withdrawing group, *e.g.* **145**. After addition of excess methyl acrylate (3 equiv.), the resulting solution was warmed to RT then heated at reflux for 12 h. After work-up of the reaction mixture, none of the desired product **170** was isolated (Scheme 70). The major isolated product (82% yield) was the 1,3-dibenzyltetrahydroimidazol-2-one **161a**, presumably derived from hydrolysis of the salt **162**. The use of other bases, such as LDA, DBU and *tert*-BuLi, produced similar results with isolation of **161a** varying from 67% to 80%. Moreover, the use of other solvents such as toluene and more polar solvents such as DMSO also proved unsuccessful; once again **161a** was isolated as the major product.



Scheme 70

A comparable result was obtained when we subjected the nitrogen-substituted dihydroimidazole salt 1,3-dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolium trifluoromethanesulfonate **164** to this procedure. Thus, a THF solution of 1,3-dibenzyl-2-

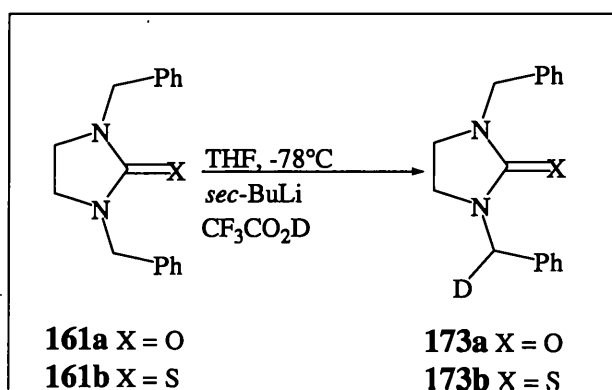
(tetramethyleneimino)tetrahydroimidazolium trifluoromethanesulfonate **164** was treated with *sec*-BuLi (1.2 equiv.) at -78°C under nitrogen. The resulting solution was stirred for 20 min at -78°C , then excess methyl acrylate (3 equiv.) was added and the solution heated at reflux for 8 h. However, purification of the crude reaction residue by silica gel column chromatography afforded, as was found for the sulfur analogue, the hydrolysis product **161a** in 79% yield (Scheme 71). Similarly, the use of LDA or DBU as alternative bases, as well as an alternative solvent, such as toluene, afforded identical results, *i.e.* the major isolated product being **161a**.



Scheme 71

To determine the reason for this lack of reaction between methyl acrylate and the azomethine ylides that we assumed had been formed, we conducted a series of deuteration experiments to investigate the extent of deprotonation at the benzylic site. Thus, treatment of the parent compounds, 1,3-dibenzyltetrahydroimidazol-2-one **161a** or 1,3-

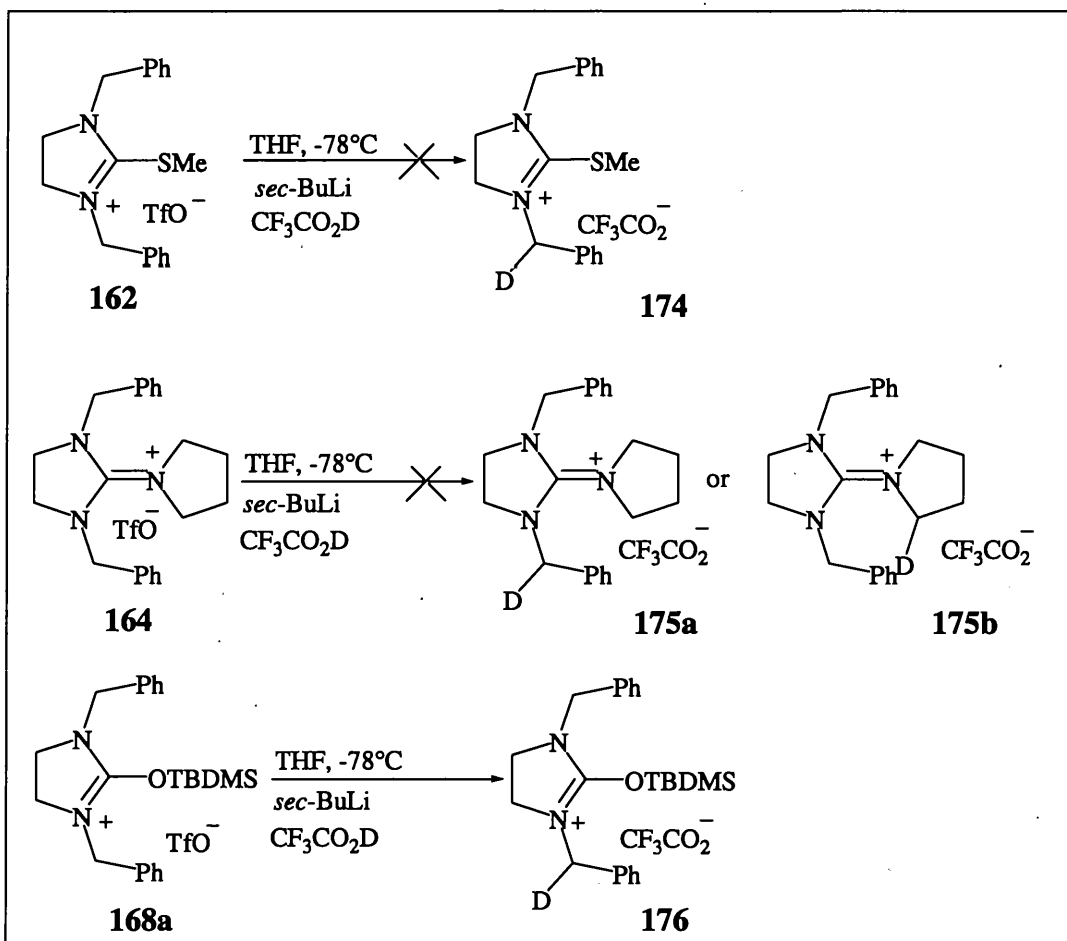
dibenzyltetrahydroimidazol-2-thione **161b**, in anhydrous THF under nitrogen at -78°C with *sec*-BuLi (1.2 equiv.) followed by the addition of deuterated trifluoroacetic acid (1 equiv.) resulted in the formation of the deuterated species **173a** and **173b** (Scheme 72). The incorporation of a deuterium atom in both substrates was supported by spectroscopic evidence. The benzylic signals in the ^1H NMR spectra of **161a** or **161b** are sharp singlets at δ 4.32 or δ 4.92, respectively, each integrating to four protons. After deuterium incorporation, the pattern of these signals changes to two singlets δ 0.03 apart, one integrating to two protons, the other to one proton, as expected for the replacement of one of the protons by a deuterium atom.



Scheme 72

This implies that it is possible to form the carbanion at the benzylic site from these compounds. We also screened other bases, such as DBU and LDA, but we were unable to detect any deuterium incorporation.

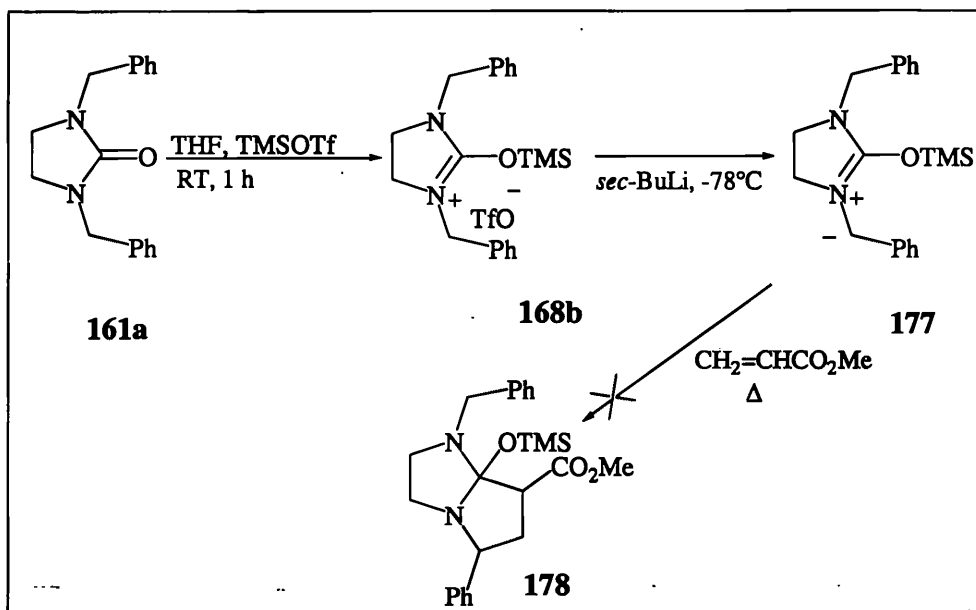
We then turned our attention to examining deuteration of the sulfur-, nitrogen- and oxygen-substituted dihydroimidazole salts, **162**, **164** and **168a**, respectively, under analogous conditions (Scheme 73).



Scheme 73

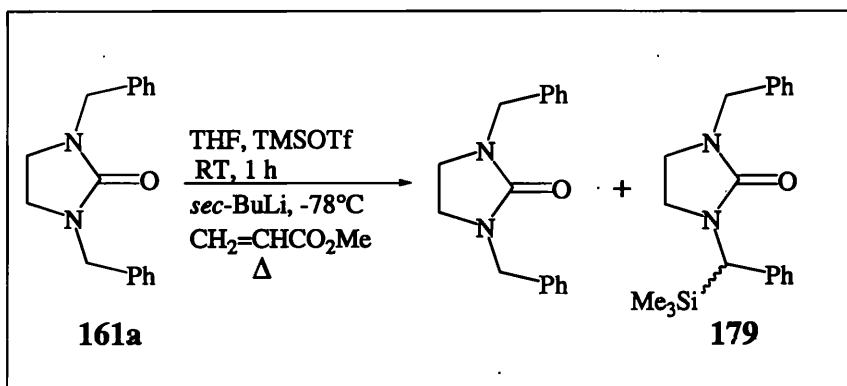
Most surprisingly, attempted deuteration of the 1,3-dibenzyl-2-methylthio-4,5-dihydroimidazolium trifluoromethanesulfonate salt **162** failed to afford the deuterated dihydroimidazole **174**; ^1H NMR analysis revealed both the pattern and integration ratio of the substrate **162** to be unchanged. Thus, it would appear that the failure of the 1,3-DC reactions involving **162** (Scheme 70) may be attributable to the non-formation of the desired azomethine ylide. Analogous results were obtained from attempts to deuterate either the benzylic position or the position α - to the nitrogen atom of the pyrrolidine ring of 1,3-dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolium trifluoromethanesulfonate

164. Thus, ^1H NMR spectroscopic analysis showed that both the pattern and integration ratio of the signals of substrate **164** were unchanged, again implying that formation of the desired azomethine ylide did not take place. The results obtained for the deuteration of the oxygen-silylated dihydroimidazole **168a** were more encouraging. According to ^1H NMR spectroscopic evidence, deuterium insertion into the benzylic site takes place since the signal corresponding to the benzylic protons of **168a** changes from a singlet integrating to four protons at δ 4.61 to two singlets separated by δ 0.03, one of which integrates to one proton and the other to two protons. Since the results were consistent with formation of the azomethine ylide from **168a**, we decided to subject the oxygen-substituted dihydroimidazoles, **167**, **168a** and **168b**, to the 1,3-DC reaction conditions. To minimize potential hydrolysis of these salts, we performed the reactions on 1,3-dibenzyltetrahydroimidazol-2-one **161a** as starting material using a one-pot method. Thus, a solution of **161a** in anhydrous THF at RT and under nitrogen was treated with TMSOTf (1.2 equiv.). After 1 h the solution was cooled to -78°C and *sec*-BuLi (1.2 equiv.) was added dropwise, and 30 min later excess methyl acrylate (3 equiv.) was added at -78°C (Scheme 74).



Scheme 74

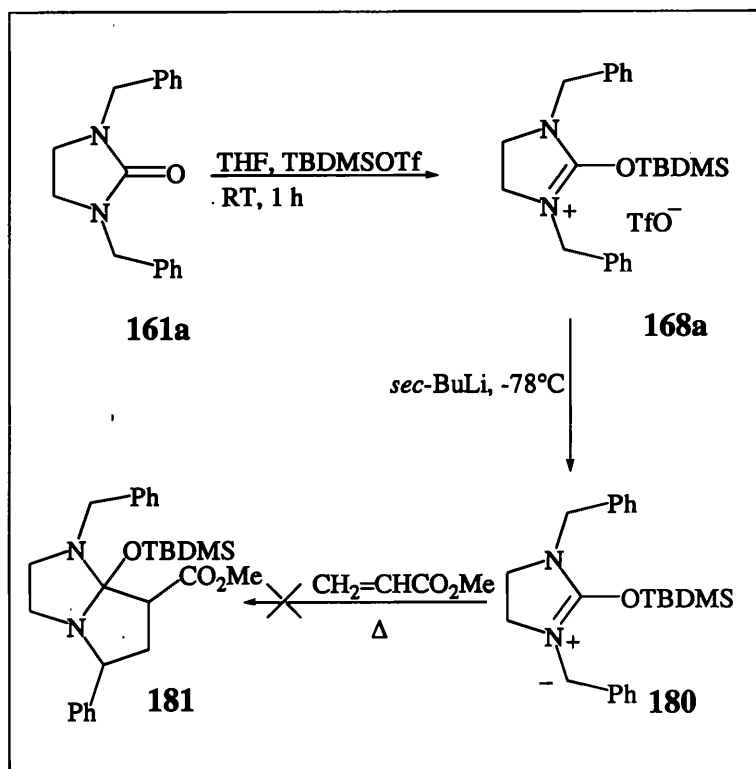
Unfortunately, the only compounds isolated from this reaction were the starting material, **161a**, in 28 % yield and the C-silylated compound **179** in 13% yield (Scheme 75). Thus, from the formation of **179** it would appear either that the ylide **177** has formed and the trimethylsilyl group has migrated from the oxygen atom to the benzylic carbon, or that the substrate **161a** is deprotonated and silylated directly.



Scheme 75

If **179** were the result of a silyl group migration in the azomethine ylide, we hoped that the use of a dihydroimidazole substrate O-silylated with a bulkier group such as in **168a** would

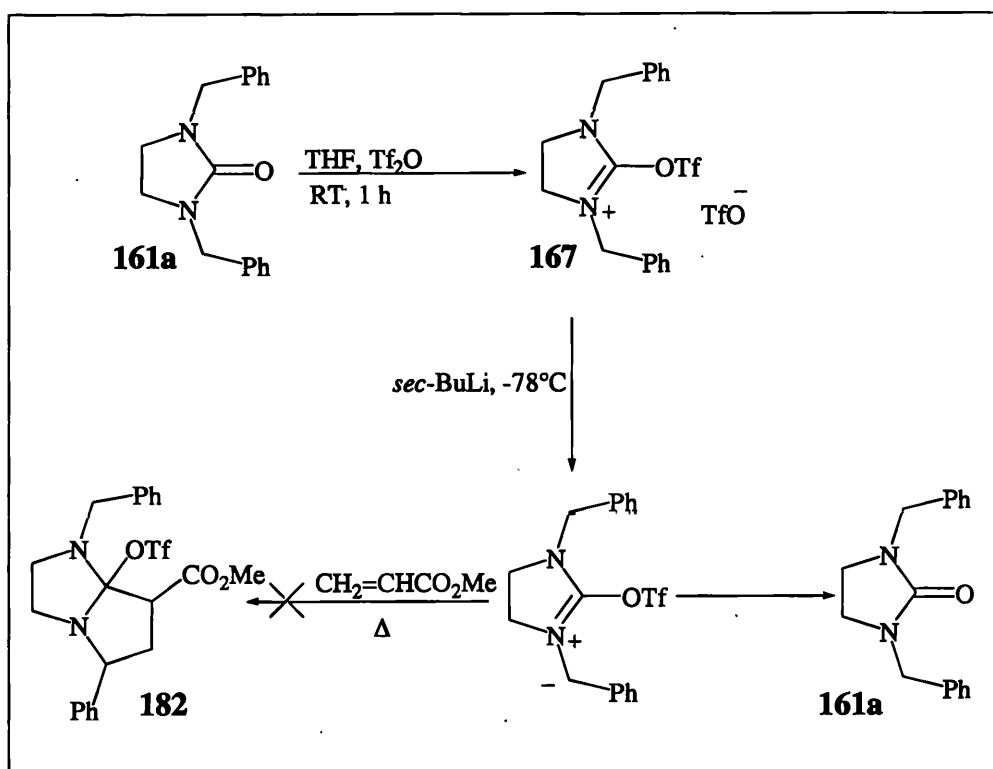
impede the rate of migration and allow the azomethine ylide to be trapped by the dipolarophile. Thus, a solution of **161a** in anhydrous THF at RT and under nitrogen was treated with TBDMSOTf (1.2 equiv.) to form the salt **168a**. The solution was cooled to -78°C and *sec*-BuLi (1.2 equiv.) was added dropwise to form the corresponding azomethine ylide **180**. Addition of excess methyl acrylate (3 equiv.) followed by purification of the crude mixture by silica gel column chromatography afforded **161a** in 78% yield as recovered starting material (Scheme 76). The use of a lower polarity solvent (toluene) afforded similar results.



Scheme 76

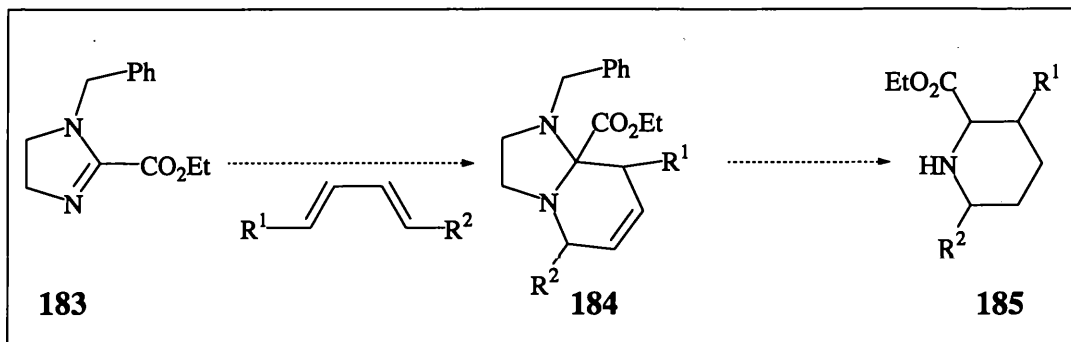
Using the same reaction conditions, the O-trifluoromethylsulfonated salt **167** was generated (using Tf_2O as sulfonating agent), and treated with *sec*-BuLi (1.2 equiv.) followed by excess methyl acrylate (3 equiv.). Once again, the expected 1,3-DC reaction

adduct **182** was not isolated, the major material recovered being the starting material **161a** in 65% yield (Scheme 77).



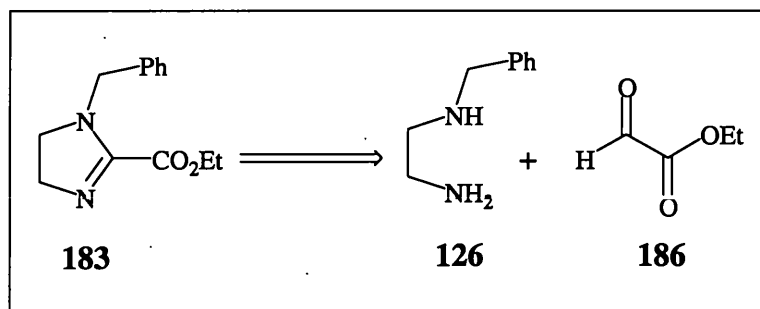
Scheme 77

As a complement to the studies described above of 4,5-dihydroimidazoles substituted at C-2 with lone-pair donor heteroatoms, and their potential as azomethine ylide precursors, we initiated preliminary studies on the introduction of electron-withdrawing substituents at C-2. The application of the so-formed substituted 4,5-dihydroimidazoles, such as **183** would have potential application to [4+2] cycloaddition reactions. We anticipated these reactions would ultimately, after 4,5-dihydroimidazole template removal and appropriate reduction of the double bond in **184**, allow access to piperidine adducts such as **185** (Scheme 78).



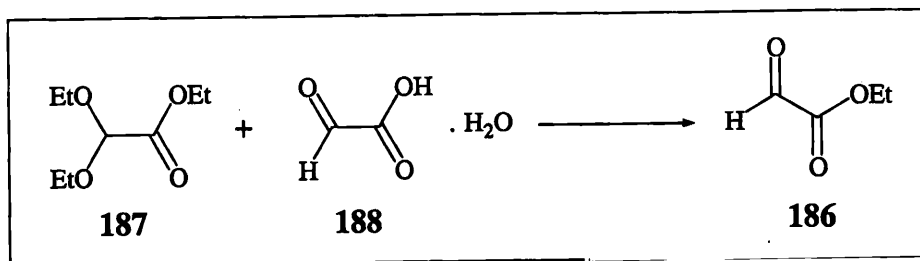
Scheme 78

Based on a reported protocol applied in benzimidazole systems,⁹⁴ we anticipated that the dihydroimidazole **183** would be accessible from the reaction of N-benzyl-1,2-diaminoethane **126** with ethyl glyoxalate **186** (Scheme 79) followed by oxidation with iodine.



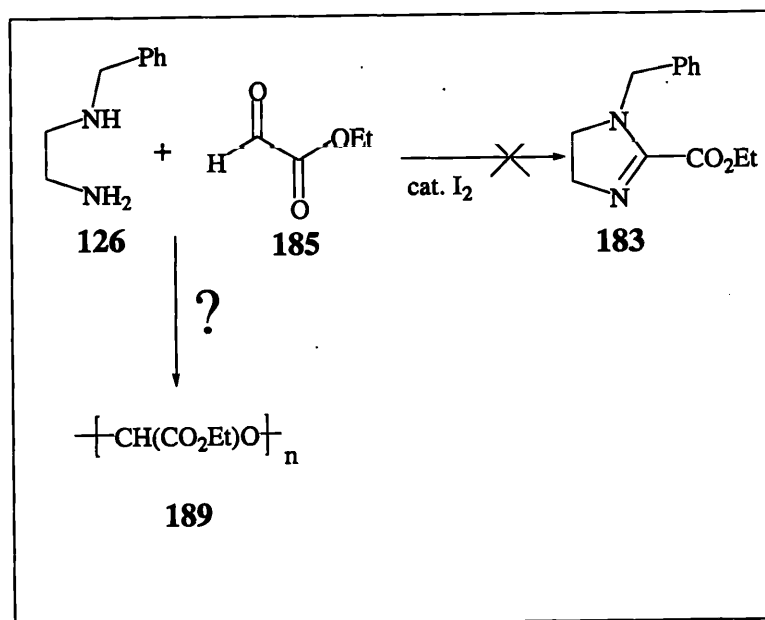
Scheme 79

N-Benzyl-1,2-diaminoethane **126** was accessible as described previously⁴² whereas ethyl glyoxalate **186** was synthesised in 89% yield by the reaction of commercial ethyl diethoxyacetate **187** with glyoxylic acid monohydrate **188** in the presence of *p*-toluenesulfonic acid (Scheme 80), as reported by Hook.⁹⁵



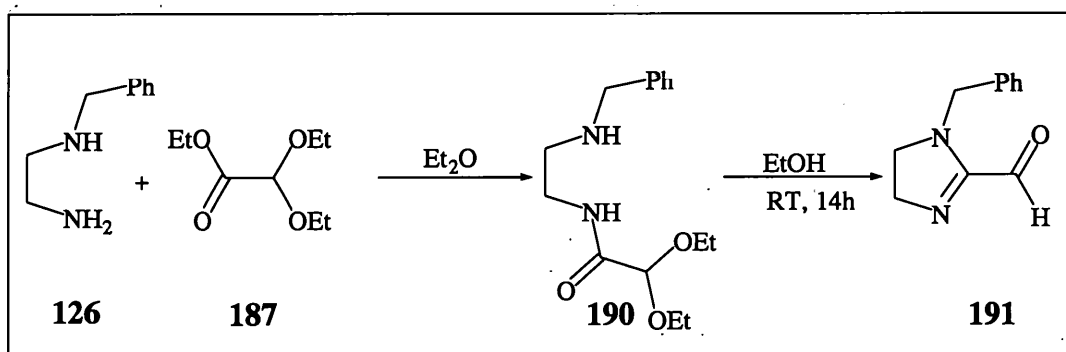
Scheme 80

However, in our hands, the reaction between a solution of ethyl glyoxalate **186** (1.2 equiv.) in toluene, and a solution of N-benzyl-1,2-diaminoethane **126** in ethanol in the presence of catalytic iodine (0.2 equiv.) did not afford the desired product. The major product of this reaction could not be adequately characterised but its ^1H NMR suggested the formation of an ethyl glyoxalate polymer such as **189** (Scheme 81). This result was unsurprising since the tendency of ethyl glyoxalate to polymerisation is well known.^{95,96}



Scheme 81

We were, however, able to access the 2-formyl analogue of **183**. This was achieved by reacting a solution of N-benzyl-1,2-diaminoethane **126** in diethyl ether with commercial ethyl diethoxyacetate **187** (1.2 equiv.) to afford, after purification by silica gel column chromatography, N-(2-benzylaminoethyl)-2,2-diethoxyethanamide **190** in 47% yield. A solution of the latter in ethanol was stirred at RT for 14 h and then quenched to afford, after purification by silica gel column chromatography, the 1-benzyl-2-formyl-4,5-dihydroimidazole **191** in 60% yield (Scheme 82).



Scheme 82

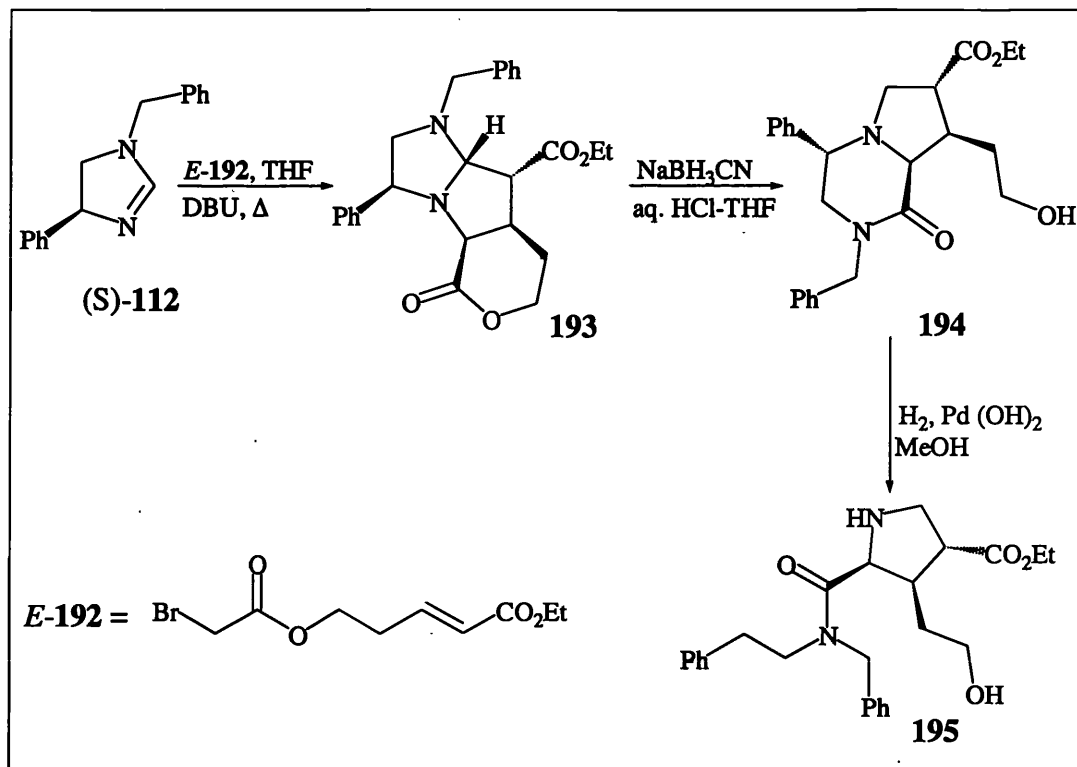
Due to time restrictions we did not have the opportunity to subject **191** to [4+2] cycloaddition conditions and the preliminary studies described above remain to be exploited. At this point we decided to conclude the 1,3-DC reaction studies of heteroatom-substituted 4,5-dihydroimidazoles and concentrate our efforts on *intramolecular* 1,3-DC reactions using novel azomethine ylides. The results and discussion of this project follow.

2.2 Intramolecular approach

This section describes the results obtained from an investigation involving the generation of novel azomethine ylides by the reaction of dihydroimidazole systems with N-alkylating agents that also contain remote alkene functionality. Since these also constitute suitable dipolarophiles they are expected to undergo *intramolecular* 1,3-dipolar cycloaddition reactions to afford heterotricyclic adducts.

2.2.1 Strategy

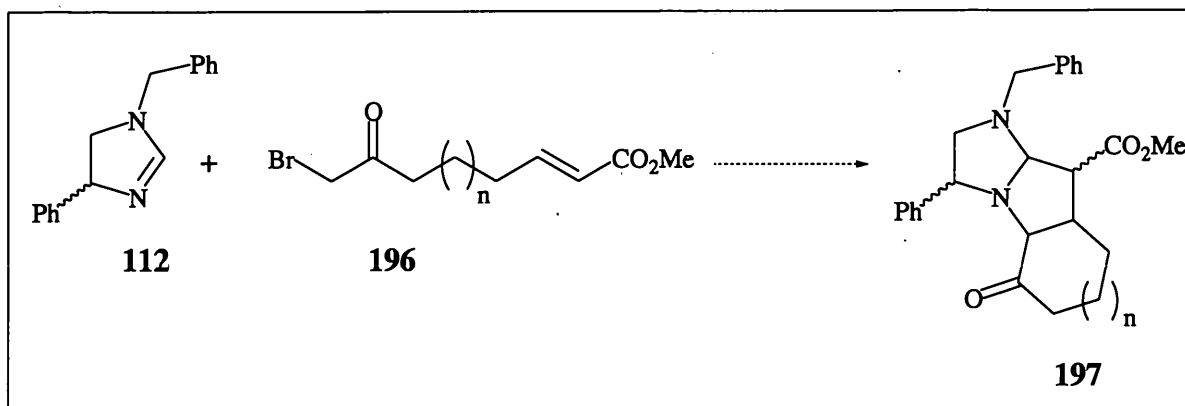
Previous researchers in our group had successfully developed a rapid and stereocontrolled *intramolecular* 1,3-DC approach to 2,3,4-trisubstituted pyrrolidines. This route employed the homochiral dihydroimidazole (*S*)-**112** as the dipole precursor and a haloalkyl reagent *E*-**192** carrying the dipolarophile (Scheme 83), that was synthesised from acrolein in four steps in moderate yield.⁹⁷ Treatment of a solution of dihydroimidazole (*S*)-**112** in anhydrous THF under nitrogen at reflux with *E*-bromoacetate ester **192**, followed by the dropwise addition of DBU as base afforded the tricyclic adduct **193** in 31% yield. The stereochemistry of the adduct is consistent with the transition state model previously postulated,⁸⁵ *i.e.* *endo* approach of the dipolarophile to the *anti*-configured dipole, with facial selectivity controlled by the 4-phenyl substituent.



Scheme 83

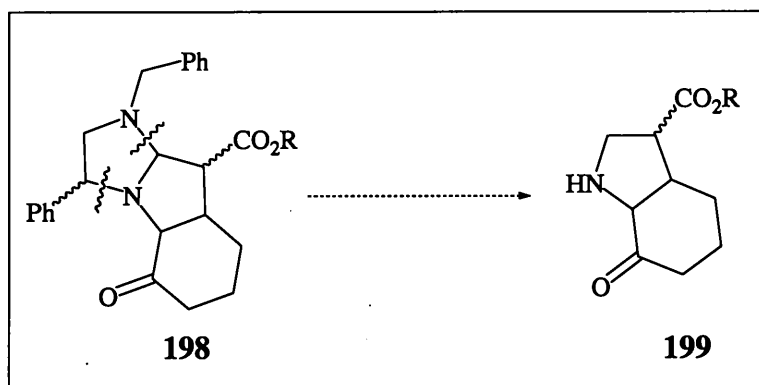
Removal of the chiral template in adduct **193** to reveal the trisubstituted pyrrolidine **195** involved amination reduction followed by hydrogenolysis of the spontaneously formed bicyclic lactam **194**.

The aim of our project involved the extension of the *intramolecular* 1,3-DC methodology depicted in Scheme 83 to an all-carbon tethered dipolarophile **196**, *i.e.* using an α -haloketone rather than an α -haloester, which it was anticipated would lead to a tricyclic product such as **197** (Scheme 84).



Scheme 84

Removal of the dihydroimidazole template, perhaps using the conditions described in Scheme 83 for **193**, should enable us to access reduced indole derivatives such as **199**, from adducts such as **198** (Scheme 85), which share the original indole skeleton of marine natural products such as Aeruginosin 98-C **200** (Figure 21). Compounds such as Aeruginosin **200** constitute new protease inhibitors, which have recently become the focus for extensive research.⁹⁸⁻¹⁰⁰



Scheme 85

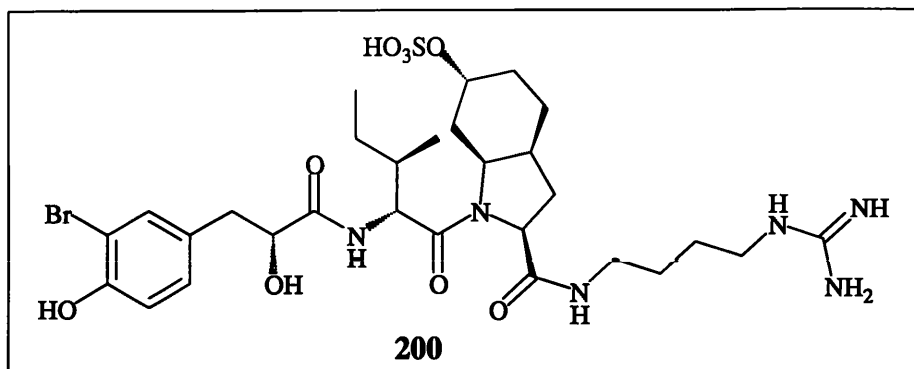


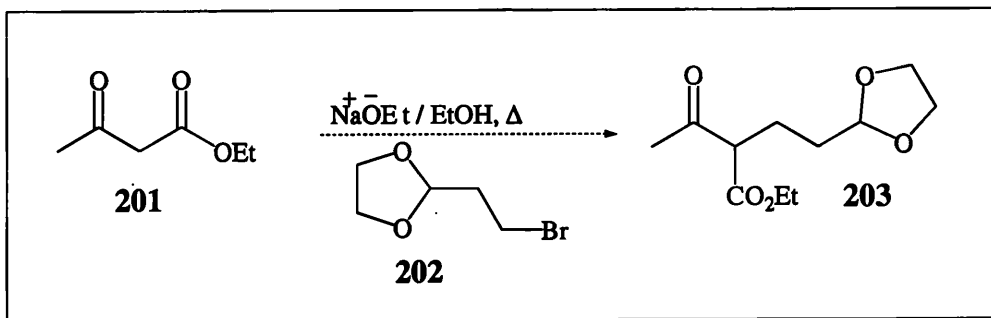
Figure 21: Aeruginosin 98-C

2.2.2 Syntheses of the α -haloketone dipolarophiles and their 1,3-dipolar cycloaddition reactions.

It was anticipated that variation of the chain length of the α -haloketone **196** would allow access to smaller and larger carbocyclic ring derivatives of **198**. Investigation of different R groups in the ester would also be addressed. Since the synthesis of either enantiomer of 1-benzyl-4-phenyl-2-imidazoline **112** had been successfully developed by previous researchers in our group,⁸⁴ our efforts were focused both on the development of a suitable approach towards the synthesis of the α -haloketones N-alkylating agents **196** and also suitable 1,3-DC reaction conditions that would allow the formation of the adducts.

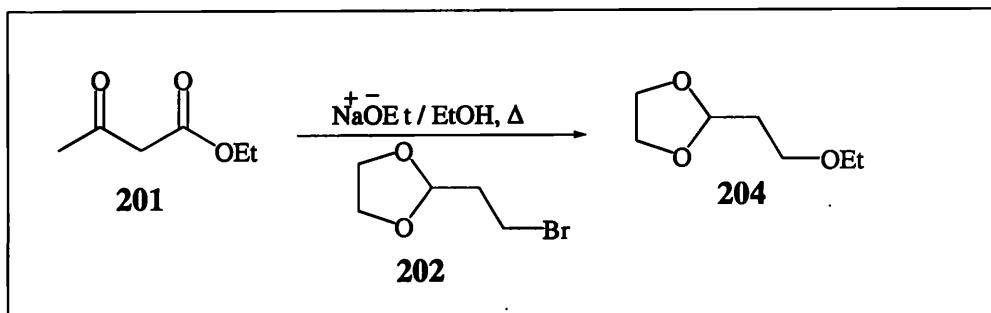
A few examples of synthetic approaches towards the synthesis of the α -haloketone **196** had been previously reported,¹⁰¹⁻¹⁰⁴ but after consideration of yields, starting material availability and the length of the synthesis, we decided to adopt the methodology developed by Grigg *et al.*¹⁰⁵ According to these workers, treatment of a solution of ethyl acetoacetate **201** in anhydrous ethanol with sodium ethoxide (1.2 equiv.) to afford the

intermediate enolate followed by the dropwise addition of commercial 2-(2-bromoethyl)-1,3-dioxolane **202** at reflux is reported to afford 2-(3-ethoxycarbonyl-4-oxopentyl)dioxolane **203** (Scheme 86).



Scheme 86

However, in our hands the reaction conditions established by these workers did not afford the desired product. Instead, we isolated 2-(2-ethoxyethyl)-1,3-dioxolane **204** in 20% yield, derived from the nucleophilic substitution reaction of ethoxide anion with 2-(2-bromoethyl)-1,3-dioxolane **202** (Scheme 87).

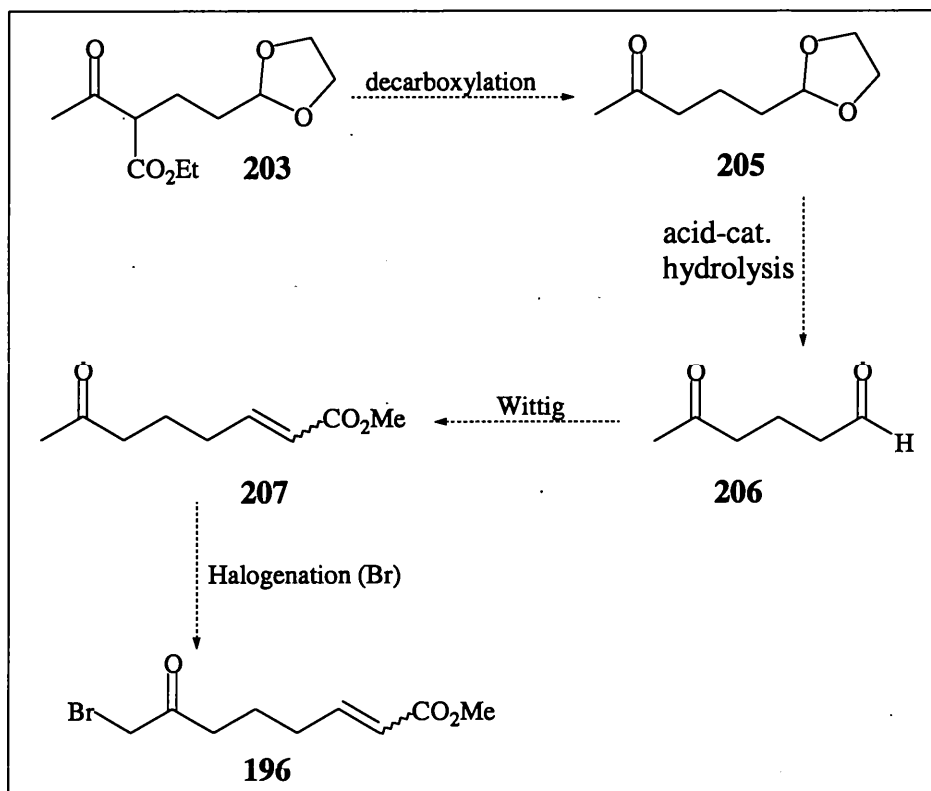


Scheme 87

We did, however, overcome this problem by substituting sodium hydride for sodium ethoxide and using THF as solvent, obtaining the desired product **203** in 45% yield.

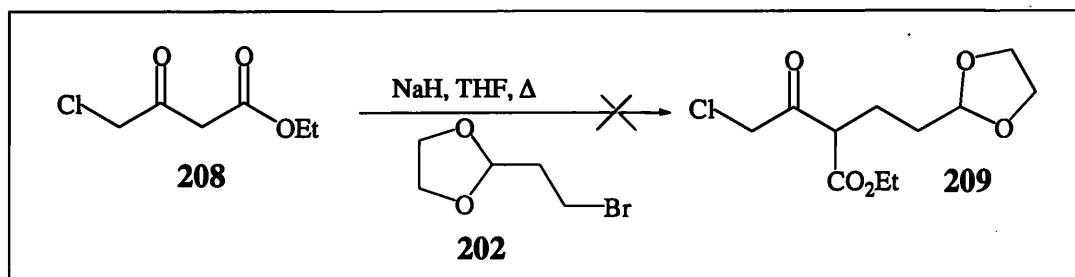
Attempts to optimise the yield of this reaction by using higher boiling solvents such as tetrahydropyran (THP) and diglyme afforded identical results.

Since the proposed synthesis (Scheme 88) of the dipolarophile precursor **196** would need to include halogenation, to incorporate the α -haloketone N-alkylating agent,



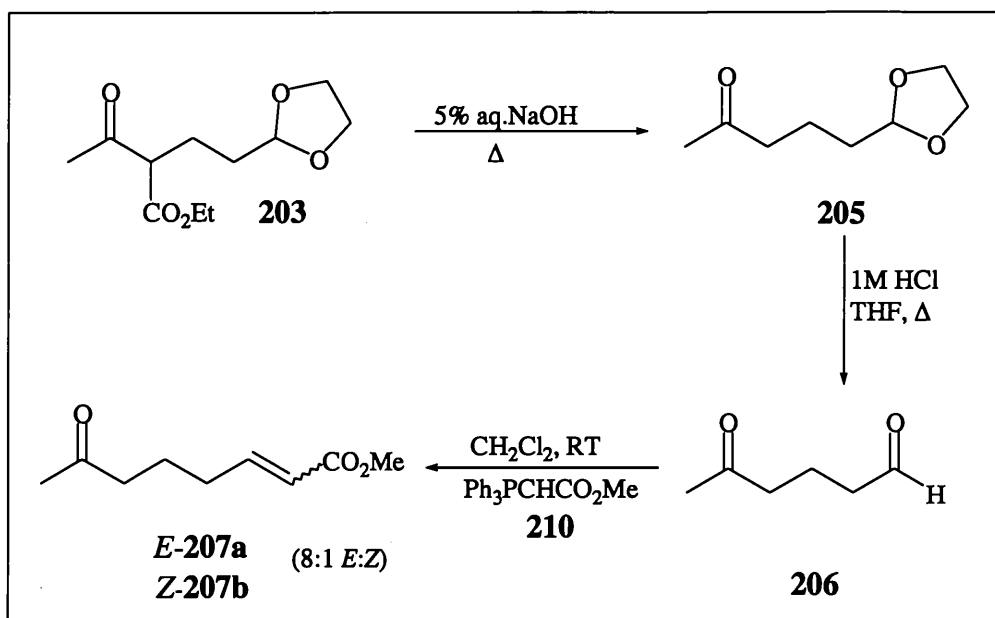
Scheme 88

we envisaged the use of ethyl 4-chloroacetoacetate **208** as an alternative starting material (Scheme 89), thus resolving the issue of halogenation directly in the first step of our dipolarophile synthesis (Scheme 88). However, by thin layer chromatography we did not observe the formation of a new product from the reaction of **208** with **202**; moreover, subjection of the crude residue to silica gel column chromatography afforded starting material **208** in 91% yield and not the expected 2-(5-chloro-3-ethoxycarbonyl-4-oxopentyl)dioxolane **209**.



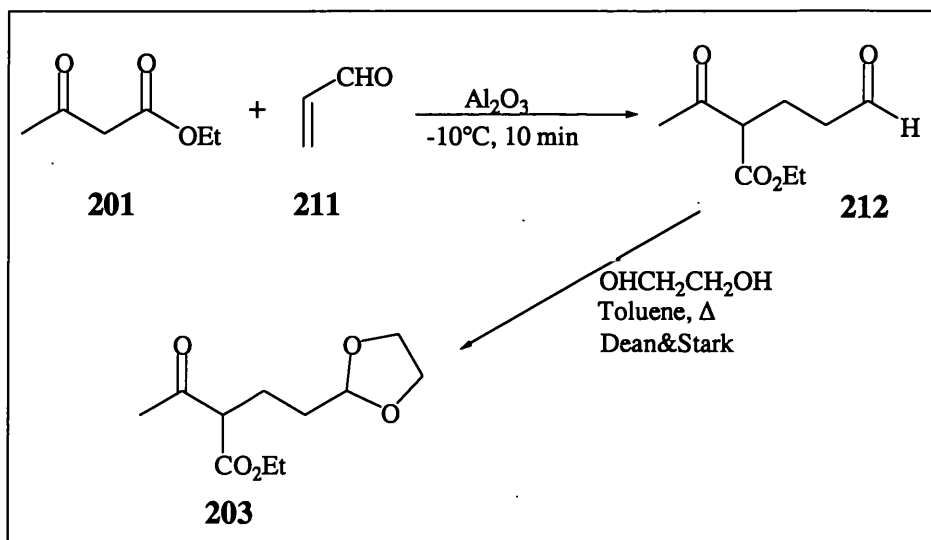
Scheme 89

Consequently, we resumed the synthesis of **196** by the route shown in Scheme 88. Basic hydrolysis and decarboxylation of 2-(3-ethoxycarbonyl-4-oxopentyl)dioxolane **203** was achieved by heating in 5% aqueous sodium hydroxide solution at reflux for 16 h to afford the desired 2-(4-oxopentyl)dioxolane **205** in 89% after purification. Acid-mediated acetal cleavage was accomplished by treating an ice-cold solution of **205** in THF with 1M hydrochloric acid (3 equiv.), and heating the resulting solution to 50°C for 5 h, giving the desired aldehyde, 5-oxohexanal **206** in 79% yield. The latter was subjected to Wittig olefination in anhydrous dichloromethane with freshly prepared methyl (triphenylphosphoranylidene)acetate¹⁰⁶ **210** in dichloromethane at RT for 18 h to afford methyl 7-oxooct-2-enoate in 90% yield as an 8:1 mixture of *E*- and *Z*- isomers (**207a** and **207b**, respectively) which were separable by silica gel column chromatography (Scheme 90).



Scheme 90

By changing the solvent of the Wittig reaction from dichloromethane to ethanol we were also able to affect the ratio of the isomeric products **207a**:**207b** from 8:1 in favour of the *E*- isomer to a 1:1 isomeric ratio, thus giving better access to the *Z*-isomer. Although the use of this approach allowed us ready access to our dipolarophile precursors **207a** and **207b**, we decided to investigate an alternative route to these since the 2-(2-bromoethyl)-1,3-dioxolane **202** starting material is expensive. We were able to achieve this by treating ethyl acetoacetate **201** with acrolein **211** (1 equiv.) at -10°C (ice-methanol bath) in the presence of activated alumina (Al_2O_3) for 10 min which gave the keto-aldehyde **212** in 80% yield as the product of a Michael addition.¹⁰⁷ Acid-catalysed acetal protection of the aldehyde moiety of **212** using ethylene glycol¹⁰⁸ and Dean-Stark azeotropic removal of water afforded 2-(3-ethoxycarbonyl-4-oxopentyl)dioxolane **203** in 70% yield (Scheme 91). Unfortunately, attempts to scale-up the reaction using more than 1 g of starting material invariably resulted in a considerable decrease in the yields of both synthetic steps, rendering this approach impractical.

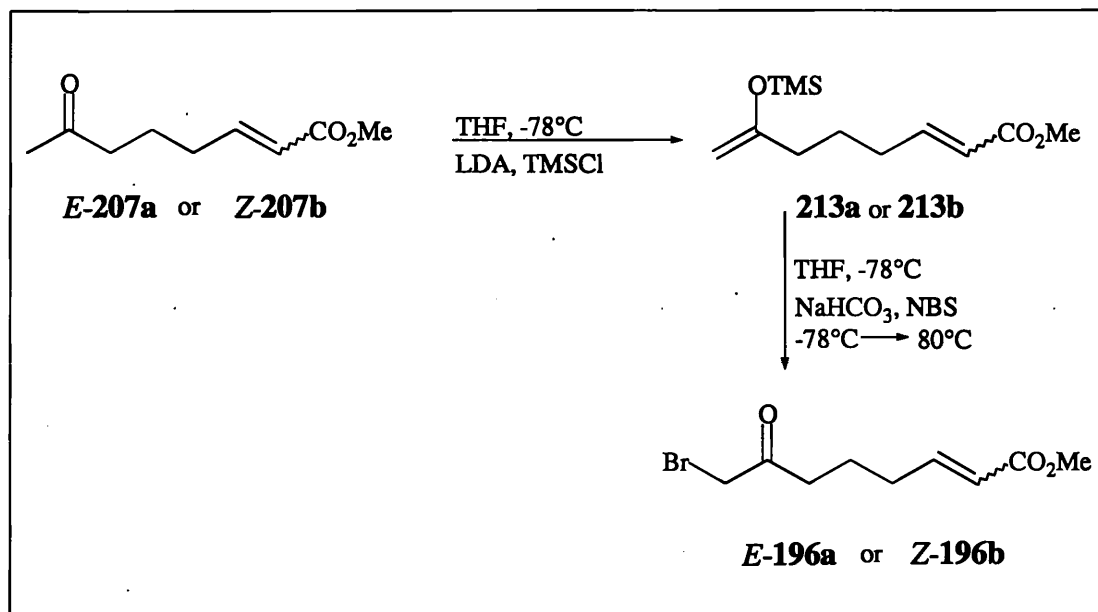


Scheme 91

We therefore employed the original approach, using commercial 2-(2-bromoethyl)-1,3-dioxolane **202**, throughout the remainder of the project.

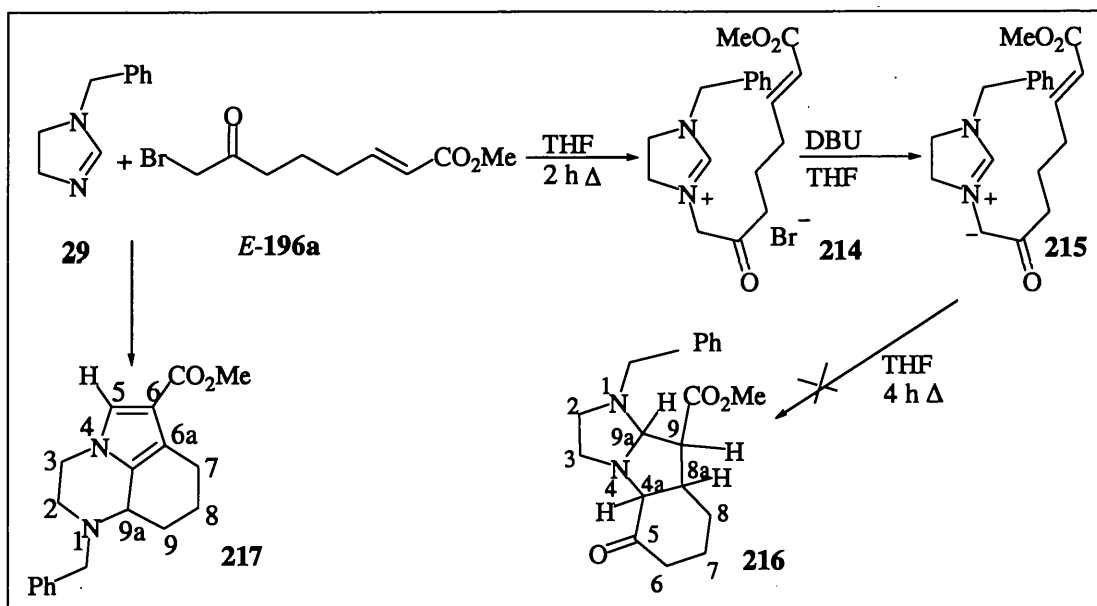
Having synthesised **207a** and **207b** we now needed to develop a protocol for the regioselective halogenation of these compounds at the methyl carbon α - to the ketone, *i.e.* the least hindered site. To that end, we envisaged the formation of the kinetic enolate followed by quenching with a mild electrophilic brominating agent such as *N*-bromosuccinimide. Thus, treatment of a solution of either **207a** or **207b** in anhydrous THF under nitrogen at -78°C with a solution of LDA in anhydrous THF, freshly prepared from *n*-BuLi and diisopropylamine (1.2 equiv.), also at -78°C generated the kinetic enolate anion. This anion was quenched by the addition of excess chlorotrimethylsilane (5 equiv.) in anhydrous THF at -78°C to form the *E*- and *Z*- isomers silyl enol ethers **213a** and **213b** in 79% yield. When these were treated in anhydrous THF at -78°C under nitrogen with solid NaHCO_3 (1.4 equiv.) followed by portionwise addition of NBS (1.3 equiv.) as brominating agent and then heating the mixture to 80°C for 2 h, both methyl *E*-8-bromo-7-

oxooct-2-enoate **196a** (from **207a**) and methyl Z-8-bromo-7-oxooct-2-enoate **196b** (from **207b**) were afforded in 45% combined yield (Scheme 92). We found that it was absolutely crucial for the success of this reaction for all reagents and solvents to be meticulously dry as well as all glassware flame dried.



Scheme 92

Having synthesised the required alkylating agents, viz. methyl *E*-8-bromo-7-oxooct-2-enoate **196a** and methyl *Z*-8-bromo-7-oxooct-2-enoate **196b** we proceeded to investigate their *intramolecular* 1,3-DC reactions with dihydroimidazoles. Thus, adopting the intermolecular 1,3-DC reaction conditions discussed in Chapter 1, 1-benzyl-4,5-dihydroimidazole **29**, synthesised from 1,2-diaminoethane **125** by N-alkylation with benzyl chloride followed by ring closure using triethyl orthoformate,⁴² was heated with methyl *E*-8-bromo-7-oxooct-2-enoate **196a** in THF at reflux followed by dropwise addition of DBU over 4 h and reflux for a further 4 h, to afford a product that was not the expected cycloadduct **216** (Scheme 93).



Scheme 93

Firstly, the mass spectrum had a molecular ion at m/z 310 rather than the expected m/z 328 for **216**. Secondly, the ^1H NMR spectrum contained a 1H singlet at δ 7.12, reminiscent of an aromatic proton, and the anticipated doublets at δ 3.86 and δ 4.65 for the 4a-CH and 9a-CH protons⁹⁷, respectively, for **216** were absent. Thirdly, the ^{13}C NMR spectrum did not contain the expected ketone carbon signal at about δ 200-210. Furthermore, DEPT ^{13}C NMR analysis showed the presence of only two CH carbon atoms at δ 59.7 and δ 124.3 in contrast to the expected four CH for **216**. One other feature stands out in the ^1H NMR spectrum (Figure 22); namely, not only are the benzylic methylene protons diastereotopic (two separate doublets at δ 3.12 and δ 4.24) but also every other CH_2 proton is magnetically unique. This implies the molecule does contain at least one chiral centre. Finally, four signals in the ^{13}C NMR spectrum at δ 113.8, δ 117.0, δ 124.3, δ 130.2 are consistent with the presence of an aromatic ring; that at δ 124.3 bears the hydrogen atom

that gives rise to the δ 7.12 signal in the ^1H NMR spectrum, the others are singlets observed in the region expected for a pyrrole ring.

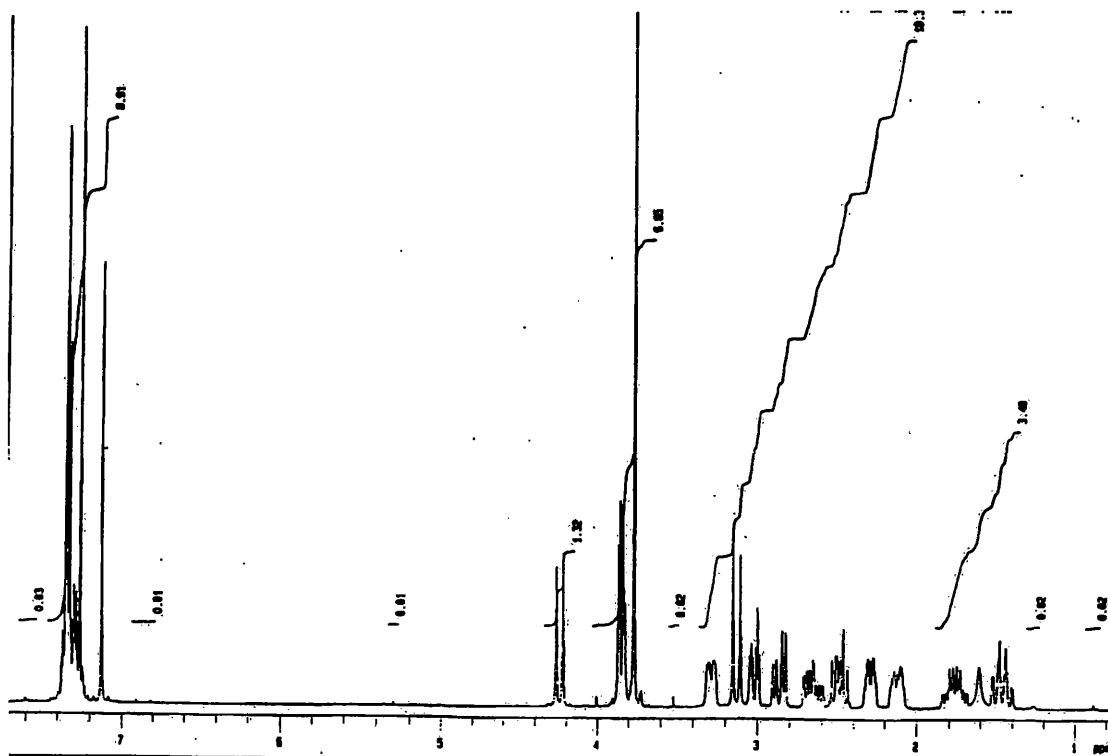
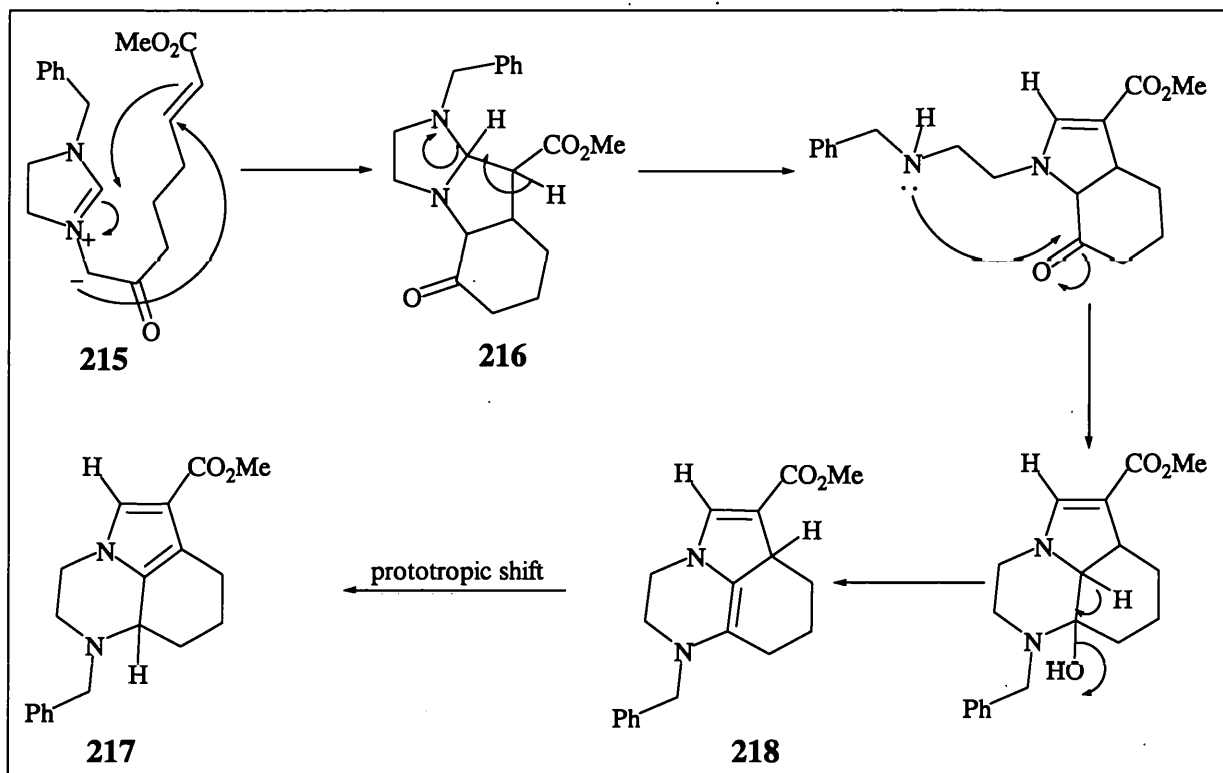


Figure 22: ^1H NMR of compound **217**.

On the basis of these spectroscopic data we assigned the structure of this as product methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate, **217**. The compound was isolated in 31% yield (Scheme 93).

The formation of the unexpected pyrroloquinoxaline **217** can be rationalised rationalized as shown in Scheme 94.



Scheme 94

We propose initial formation of dipole **215** and 1,3-dipolar cycloaddition as expected to form **216**. Eliminative ring-opening of the primary adduct **216** and closure of the liberated secondary amine onto the ketone carbonyl group^{42,97} with loss of water leads to the formation of the enamine **218** (or regioisomer). Subsequent prototropic shift leads to the aromatic pyrrole substructure and formation of **217**.

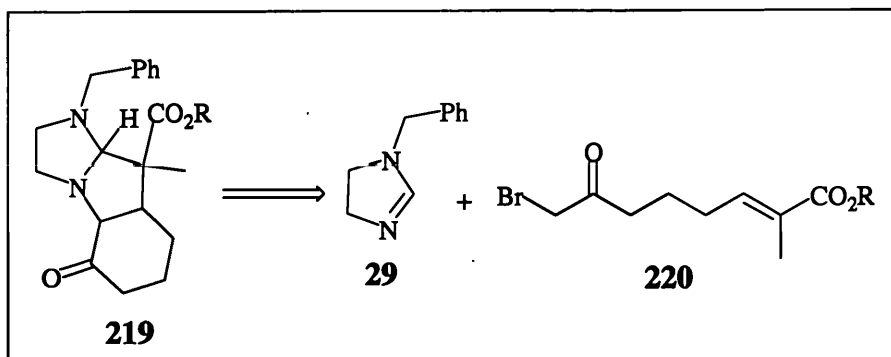
In order to investigate whether the eliminative process shown in Scheme 94 was base catalysed, we performed the reaction under base deficiency conditions (0.7 equiv.). However, the same product **217** was nonetheless isolated. Given that acid catalysis was also a possible cause for this eliminative process, we repeated this reaction and analysed the crude mixture prior to silica gel column chromatography (since silica could provide the acidic environment that might catalyse the process). However, ¹H NMR analysis of the crude mixture shows the presence of the pyrrolo proton signal at δ 7.12 and the absence of

any signals anticipated for the cycloadduct **216**, implying that the eliminative process must be structurally inherent in the primary cycloadduct **216**.

In these reactions we found that it was essential to heat the solution containing **29** and *E*-**196a** at reflux for at least 2 h prior to the addition of DBU, presumably to enable the intermediate N-alkylated salt **214** (Scheme 93) to form. Addition of DBU before 2 h invariably led to the recovery of starting materials **29** and *E*-**196a**.

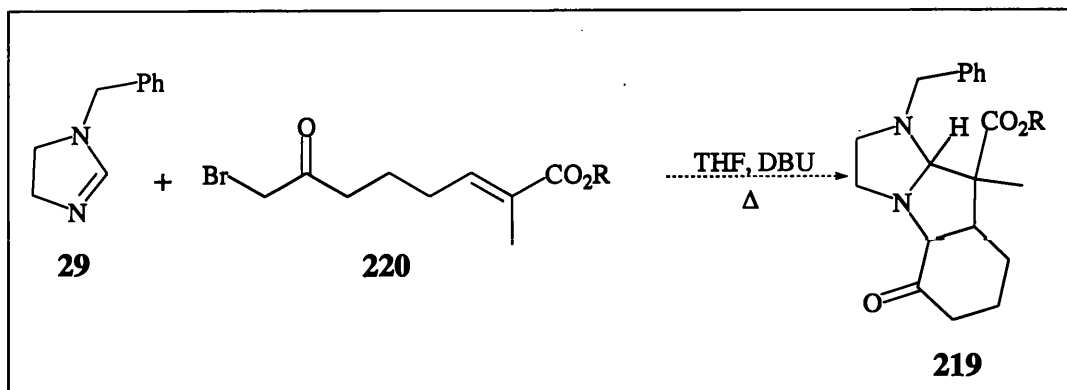
As would be expected based on the mechanism of Scheme 94, the same pyrroloquinoxaline **217** was also isolated (20% yield) when the diastereomeric *Z*-dipolarophile **196b** was used in the reaction.

To block the eliminative ring-opening of the primary adduct **216**, we envisaged incorporation of non-migrating methyl groups at strategic sites in the dipolarophile precursor molecules. The first example (Scheme 95), involves positioning a methyl group α - to the methoxycarbonyl group such that it would be attached to the C-9 carbon atom in **216**. This is the site from which the hydrogen is lost during initial eliminative ring-opening in **216**. This strategy necessitates the dipolarophile **220**, similar to **196a** but possessing a methyl substituent on the alkene α -to the ester group. We reasoned that this should be available from Wittig olefination of the previously synthesised 5-oxohexanal **206** (see Scheme 90) with an alkyl 2-(triphenylphosphoranylidene)propionate followed by regioselective α -bromination as described previously for the preparation of *E*-**196a**.



Scheme 95

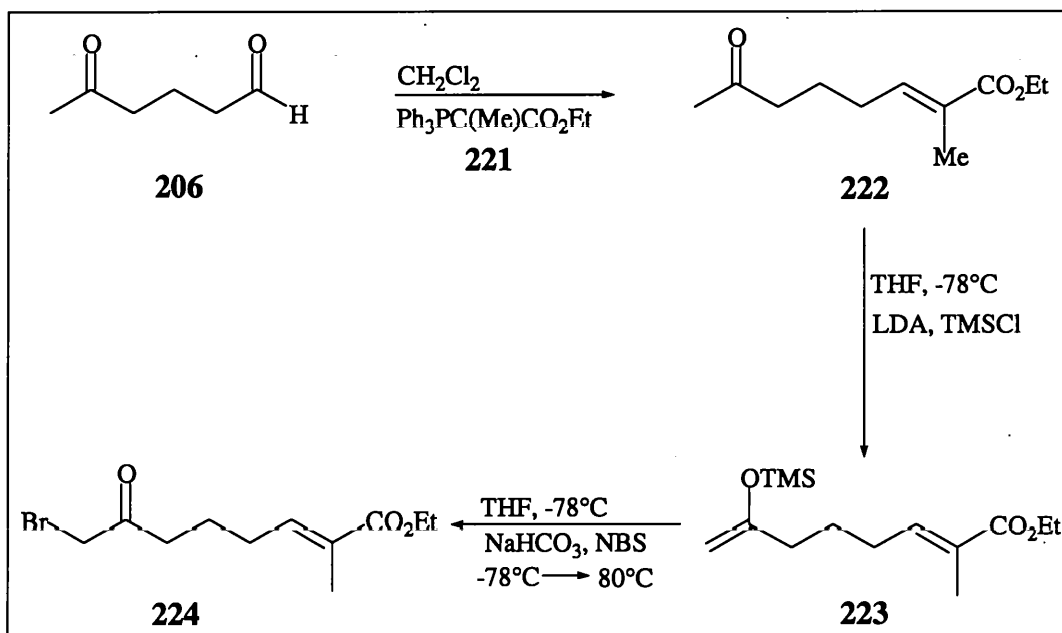
Thus, our expectation was that dipolarophile **220** would react with 1-benzyl-4,5-dihydroimidazole **29** to afford adduct **219** (Scheme 96).



Scheme 96

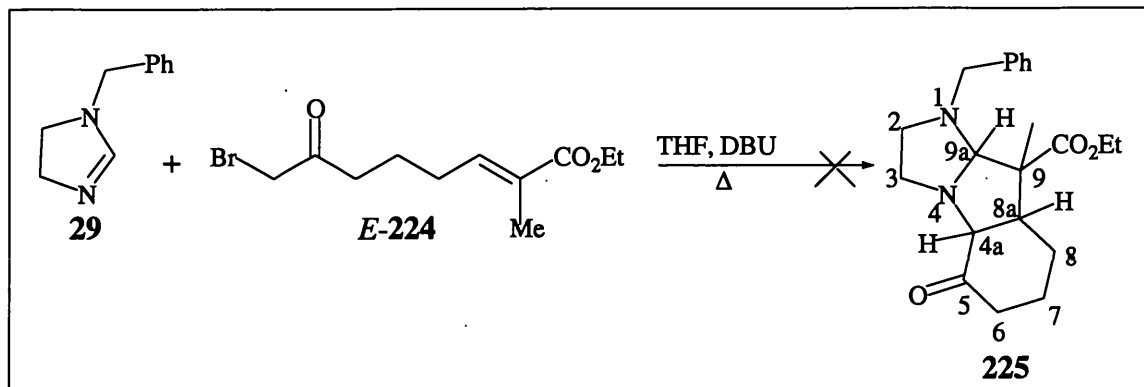
Reaction of 5-oxohexanal **206** in anhydrous dichloromethane under nitrogen at RT with commercial ethyl 2-(triphenylphosphoranylidene)propionate¹⁰⁹ **221** gave the Wittig product ethyl *E*-2-methyl-7-oxooct-2-enoate **222** in 32% yield (Scheme 97). Treatment of a solution of **222** in anhydrous THF under nitrogen at -78°C with a solution of LDA in anhydrous THF, freshly prepared from *n*-BuLi and diisopropylamine (1.2 equiv.)

generated the appropriate kinetic enolate anion which was quenched by the addition of excess chlorotrimethylsilane (5 equiv.) in anhydrous THF at -78°C to form the silyl enol ether **223**. Treatment of the latter in anhydrous THF at -78°C under nitrogen with solid NaHCO_3 (1.4 equiv.) followed by the portionwise addition of NBS (1.3 equiv.) as the electrophilic brominating agent and subsequent heating of the solution to 80°C for 2 h allowed us to isolate ethyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate **224** in 44% yield (Scheme 97).



Scheme 97

Having accessed the modified dipolarophile *E*-**224**, we were now in position to attempt the cycloaddition reaction depicted in Scheme 96, and hopefully block the eliminative ring-opening process. In the event, treatment of 1-benzyl-4,5-dihydroimidazole **29** in anhydrous THF under nitrogen at reflux with ethyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate **224** in anhydrous THF for 2 h before the dropwise addition of DBU over 4 h, and heating for a further 4 h at reflux did not afford the expected adduct **225** (Scheme 98).



Scheme 98

The ^1H NMR spectrum of the isolated product (Figure 23) showed the methylene benzylic peaks to be diastereotopic, appearing as two doublets integrating to one proton each at δ 3.43 and δ 3.90; in the starting material **29**, these appear as a singlet integrating to two protons at δ 4.29. This behaviour is consistent with the creation of a chiral centre in the molecule and, indeed, in agreement with the expected **225**. However, two crucial pieces of evidence in the ^1H NMR spectrum indicate that the isolated product was not the expected cycloadduct **225**. First, the expected doublet at δ 4-4.50 corresponding to the 9a-CH bridgehead proton⁹⁷ required in **225** was not observed. The second, and most surprising, piece of evidence was that both the alkene proton (δ 6.70, tq) and the alkene methyl peak (δ 1.83, d) from the starting material were intact, therefore implying that the alkene functionality plays no part in the formation of this unexpected product. Further, the presence of a singlet integrating to one proton at δ 9.46 in the ^1H NMR spectrum, is reminiscent of perhaps a formyl type proton (Figure 23). For **225**, the only hydrogen expected to appear as a singlet would be that at C-9a, which as mentioned previously, we would expect to appear at⁹⁷ δ 4-4.50. Another curious feature of the ^1H NMR spectrum was a triplet integrating to one proton observed at δ 3.28 with a 5Hz coupling constant, *i.e.*

characteristic of a 3J coupling constant to two protons. The 2-D ^1H - ^1H COSY NMR spectrum showed this signal to be coupled to protons in the alkene chain.

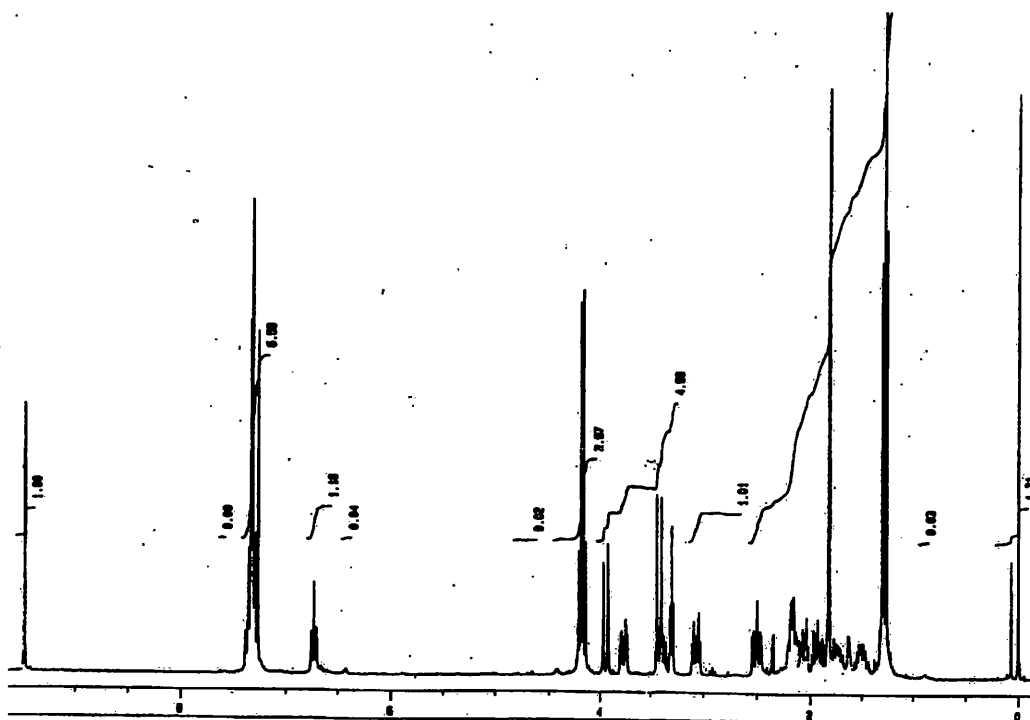
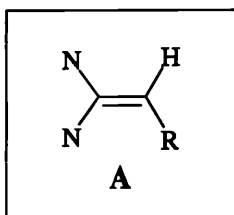


Figure 23: ^1H NMR of the product obtained from reaction of **29** with *E*-224.

The ^{13}C NMR spectrum of the product did not show the presence of a ketone carbon atom as expected for **225**. Moreover, peaks observed at δ 141.2 and δ 128.7, corresponding to the original dipolarophile alkene carbon atoms, confirmed the evidence observed in the ^1H NMR spectrum that the alkene functionality plays no part in the reaction. Two signals at δ 163.3 and δ 65.4 can be observed, which, according to DEPT-90 NMR studies, correspond to two CH carbon atoms. The former is consistent with a formyl carbon atom; the latter is due either to a CH attached to a heteroatom or, possibly, to an alkene CH such as that shown in structure **A** for which chemical shifts of approximately δ 55 have been reported.¹¹⁰



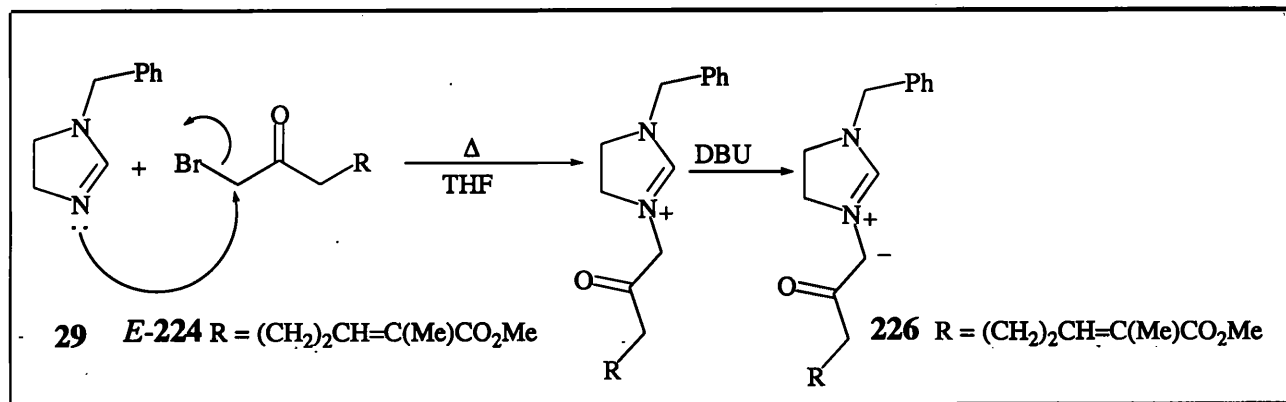
Structure A

Furthermore, a signal at δ 173.3 can also be observed (in addition to the ester at δ 168.1), which, according to DEPT-45 NMR studies, corresponds to a quaternary carbon. This could be due to the carbonyl carbon of a carboxylic acid derivative, or alternatively, to the alkene carbon atom in structure A that carries the two heteroatoms for which chemical shifts of approximately δ 165 have been reported.¹¹⁰ Low-resolution mass spectrometric analysis showed the molecular ion at m/z 344, corresponding to a twelve Dalton loss from the molecular ion expected for 225. Given that the ^{13}C NMR spectrum contains signals that account for all the twenty-one carbon atoms in the two starting materials (allowing for two aromatic CH signals arising from two pairs of equivalent carbon atoms), this twelve mass unit deficit cannot be due to loss of a carbon atom. It more likely comes about by an incorporation of a molecule of water (*i.e.* expected mass 356, plus 18, giving 374) followed by loss of a 30 Dalton fragment (*e.g.* CH_2O) to give the $\text{M}^{+\bullet}$ at 344.

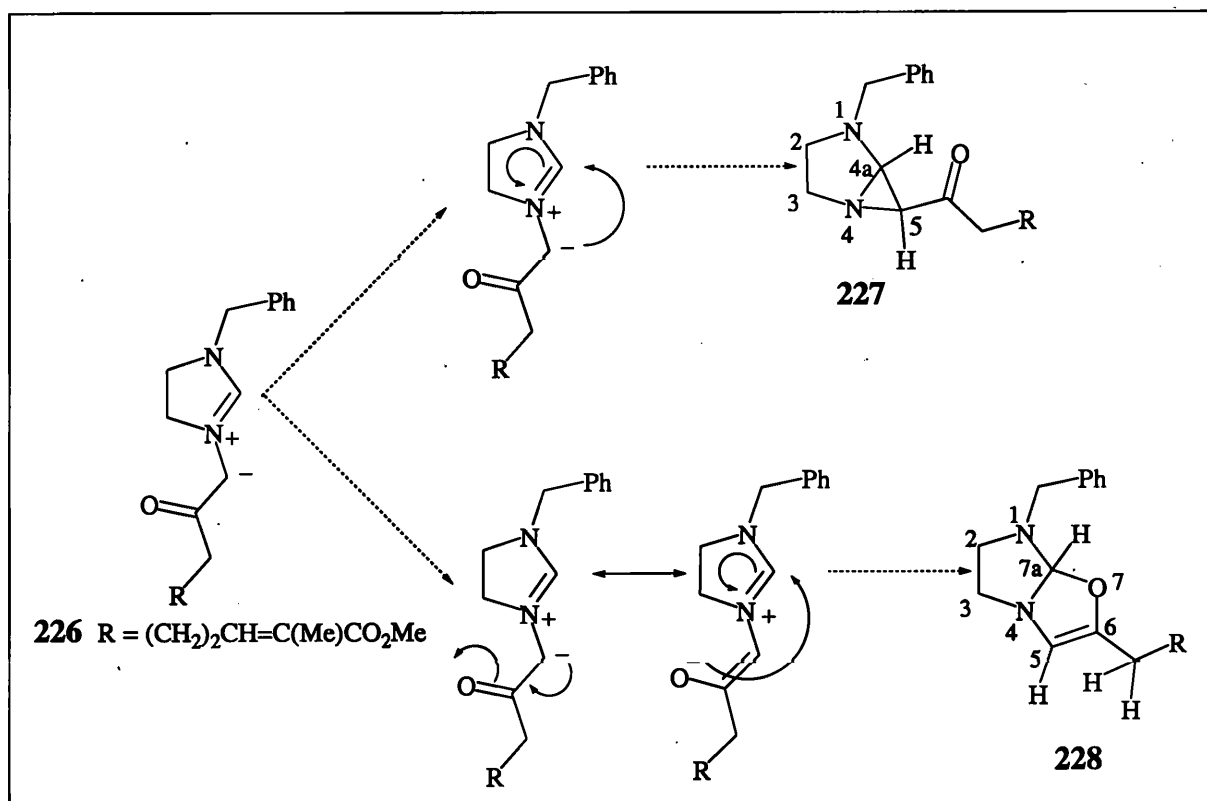
At the time of writing we have been unable to assign a definitive structure to this product, although several have been considered.[†] For example, two obvious structures (although

[†] The structure of this compound is described in the addendum on page 235

neither incorporates a water molecule) are the products from cyclisation of the ylide **226** (Scheme 99); viz., **227** and **228** (Scheme 100).



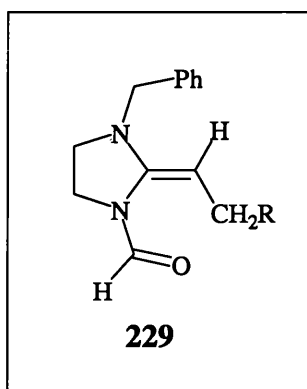
Scheme 99



Scheme 100

Both of these contain chiral centres that would account for the observed diastereotopicity. However, the aziridine hydrogen atoms in **227** should both be doublets (not observed) and neither would have the observed chemical shift values. Furthermore, the carbonyl carbon atom expected between δ 200-210 in **227** is absent from the ^{13}C NMR spectrum. Similarly, the orthoformamide proton in **228** would be a singlet and it should resonate at δ 6-7.¹¹¹ Further, the alkene CH in **228** is unlikely to resonate at δ 3.30 and the observed 5 Hz coupling is too large to be due to a 4J interaction with the adjacent CH_2 group.

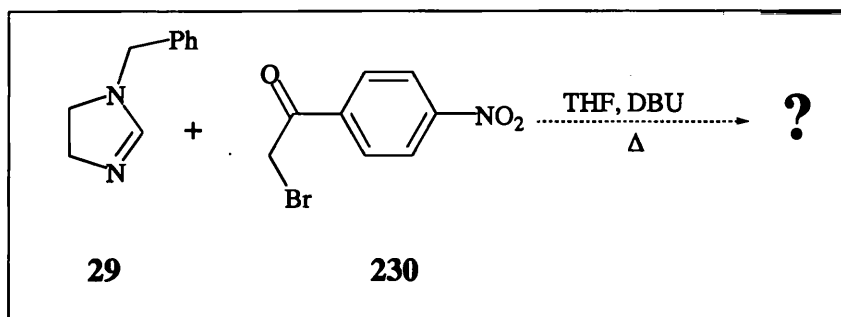
Another structure that has been considered is **229**.



This would give a close fit to the NMR spectra: there is a formyl proton and its corresponding carbonyl carbon; the alkene would give appropriate ^{13}C NMR signals at *ca.* δ 60 and δ 170; the alkene proton would be at *ca.* δ 3.5-4.0 in the ^1H NMR spectrum,¹¹⁰ and it would exhibit a triplet 3J coupling to the CH_2 group adjacent to the double bond. However, the lack of a chiral centre means that none of the CH_2 protons would be diastereotopic, a crucial feature of our isolated product.

Consequently, we decided to probe this reaction in more detail. We anticipated that the reaction of 1-benzyl-4,5-dihydroimidazole **29** with an α -haloketone chain lacking the alkene functionality would afford a product with similar but simpler spectroscopic

characteristics. In addition, by using an α -haloketone such as 2-bromo-4-nitroacetophenone **230** (Scheme 101) we hoped that a crystalline adduct would result in and hence provide us with a crystallographic analysis to settle the structural question.



Scheme 101

Thus, 1-benzyl-4,5-dihydroimidazole **29** in anhydrous THF at reflux was treated with commercial 2-bromo-4-nitroacetophenone **230** (1.2 equiv.) in anhydrous THF. Heating was continued for 2 h before the addition of DBU over a period of 4 h. Heating was continued for a further 4 h and the crude residue subjected to appropriate purification by silica gel column chromatography. The ¹H NMR spectrum of the isolated compound is shown in Figure 24. Interestingly, for this compound diastereotopicity of the benzylic methylene protons is not observed. Thus, it is unlikely that the product contains a chiral centre. However, the signal corresponding to these protons appears as two singlets at δ 3.81 and δ 3.84, of almost equal intensity and in all integrating to two protons. This type of “signal doubling” was also seen for multiplets at δ 3.06, δ 3.15, δ 3.30 and δ 3.42 (Figure 24). The total for these signals integrates to four protons and the multiplets at δ 3.06 and δ 3.42 show correlation on the ¹H-¹H COSY spectrum. Similar correlation is observed between multiplets at δ 3.15 and δ 3.30. Two other pairs of singlets are apparent;

the first at δ 6.48 and δ 6.98, the second at δ 7.90 and δ 8.27. Each integrates to one proton. This doubling of signals is strongly suggestive of the presence of a rotamer mixture.

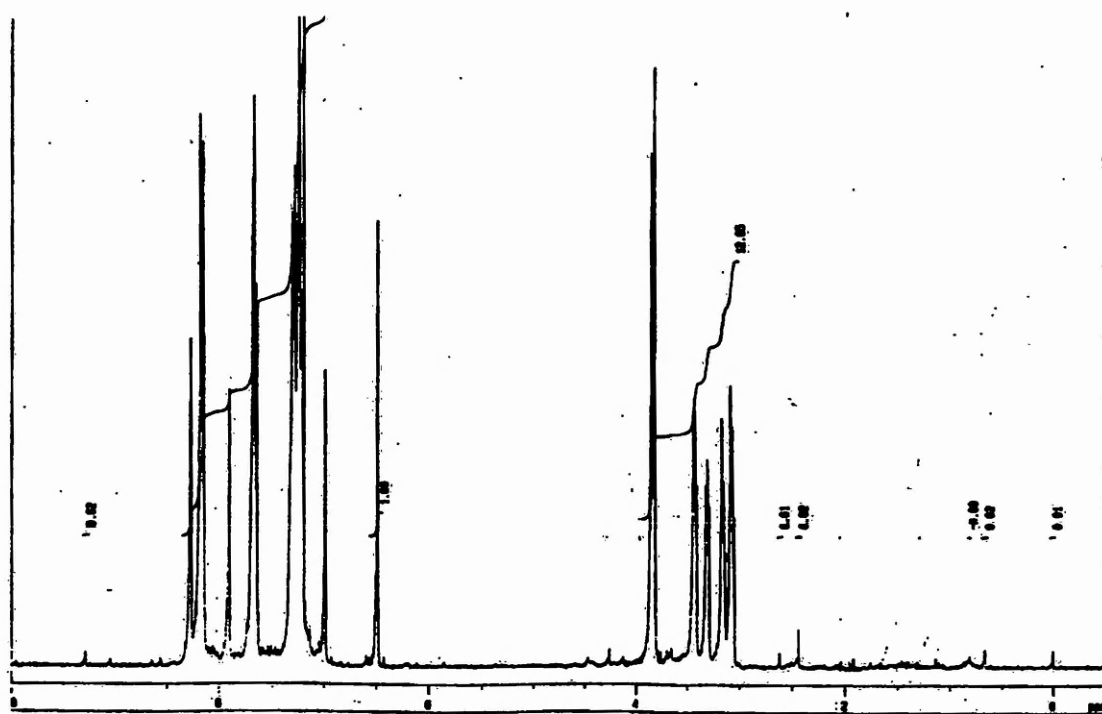
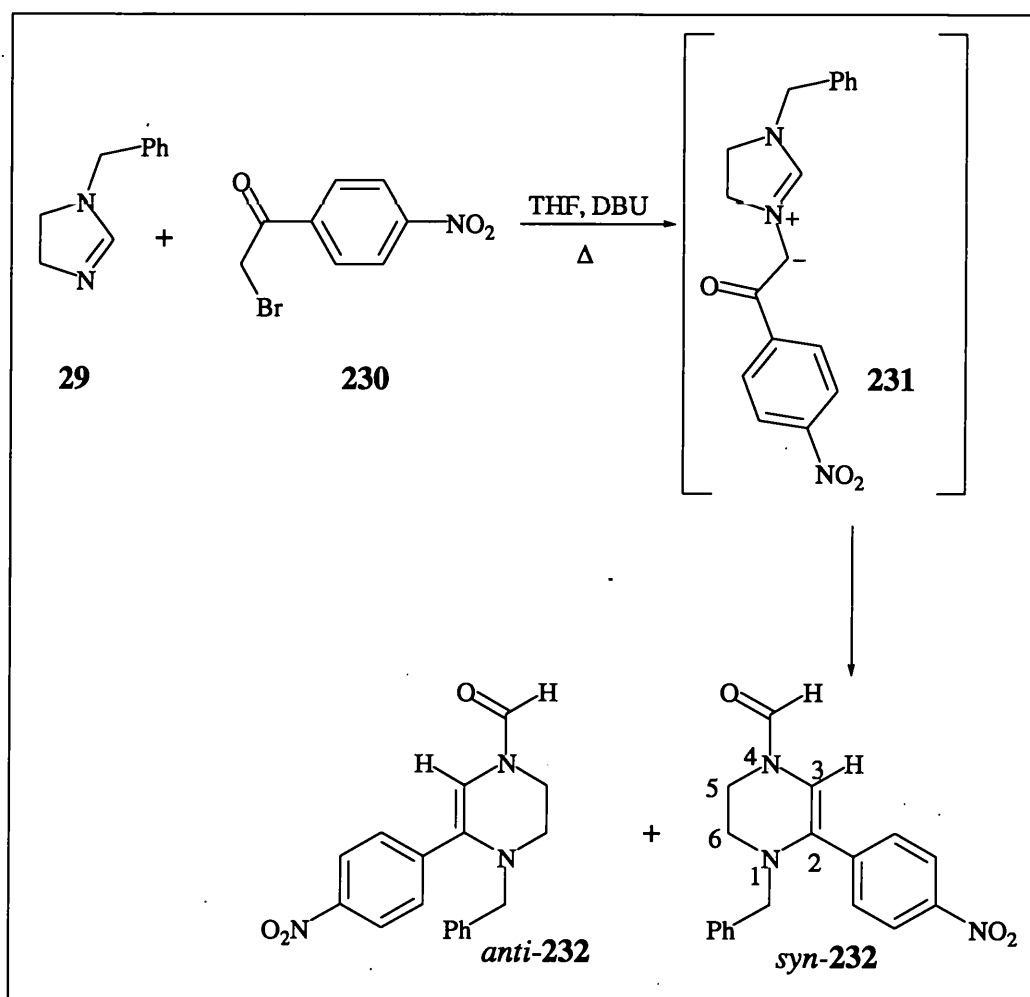


Figure 24: ^1H NMR for compound 232.

Not surprisingly, the ^{13}C NMR spectrum also displayed signal doubling. The signals observed at δ 159.3 and δ 159.9 were considered to be in the appropriate region for a formyl type carbon atom and, in addition, the pairs of signals at δ 108.6/ δ 112.2 and δ 143/ δ 147 were considered to belong to the CH and C carbon atoms, respectively, of an alkene system. Low-resolution mass spectrometry showed MH^+ at m/z 323, which is precisely the mass expected from the formation of an ylide such as 231 (Scheme 102).

On the basis of these data, we identified the product from this reaction as 1-benzyl-4-formyl-2-(4-nitrophenyl)-1,4,5,6-tetrahydropyrazine 232, isolated in 87% yield as a rotamer mixture (Scheme 102). Unfortunately, the compound is an oil, precluding X-ray crystallographic analysis.

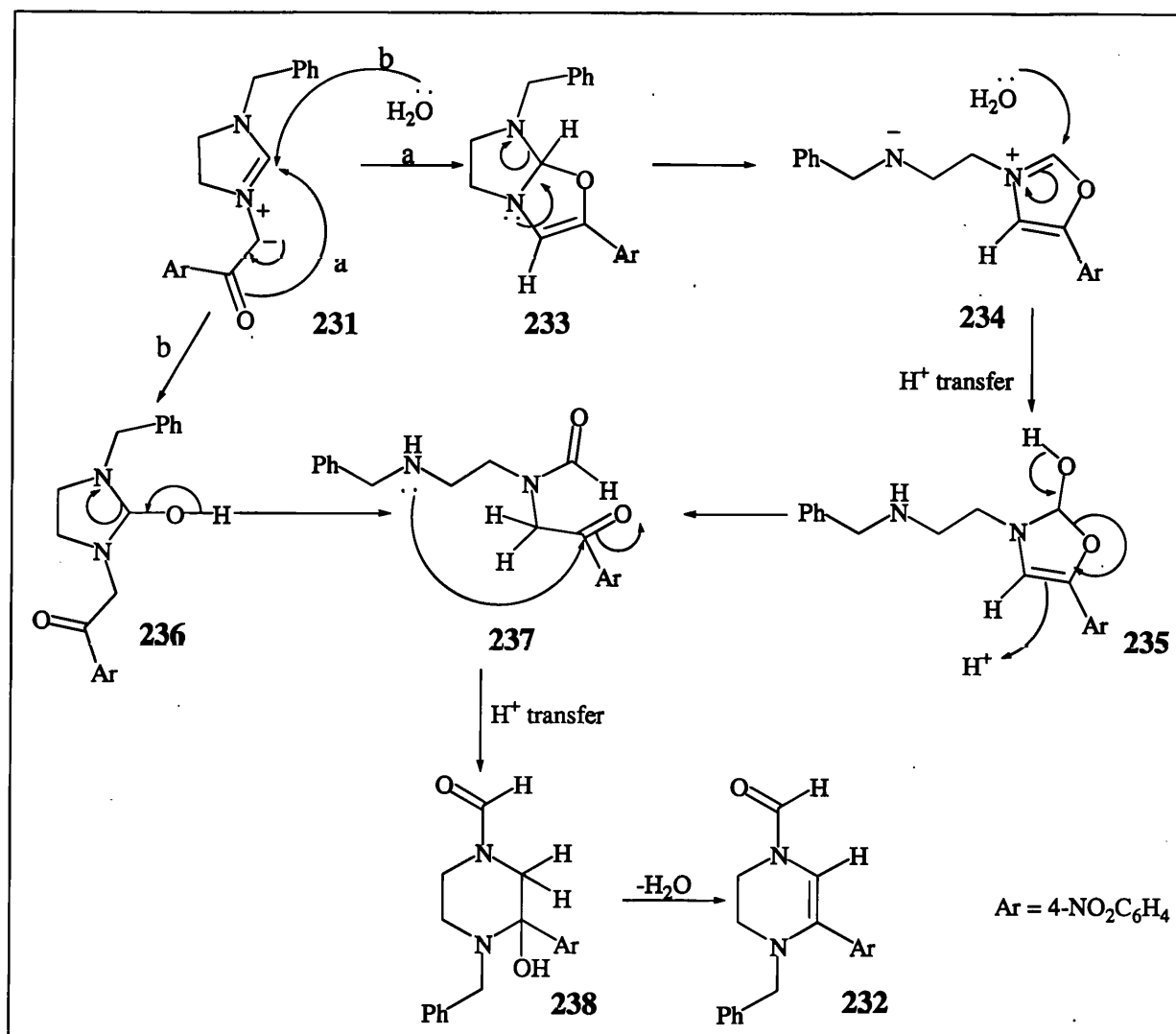


Scheme 102

The multiplets observed at δ 3.06 and δ 3.42 in the ^1H NMR spectrum can be assigned to 6- CH_2 and 5- CH_2 , respectively, of one rotamer of **232**. Similarly, the multiplets observed at δ 3.15 and δ 3.30, are assigned to the 6- CH_2 and 5- CH_2 , respectively, of the other rotamer of **232**. Presumably, the *syn* rotamer would bring about the greatest chemical shift difference between the 5- CH_2 and the 6- CH_2 protons, so we suggest the pair of signals at δ 3.06 and δ 3.42 correspond to this rotamer. The singlets at δ 3.81 and δ 3.84 are the methylene benzylic protons of each rotamer for **232**. The singlets observed at δ 6.48 and δ

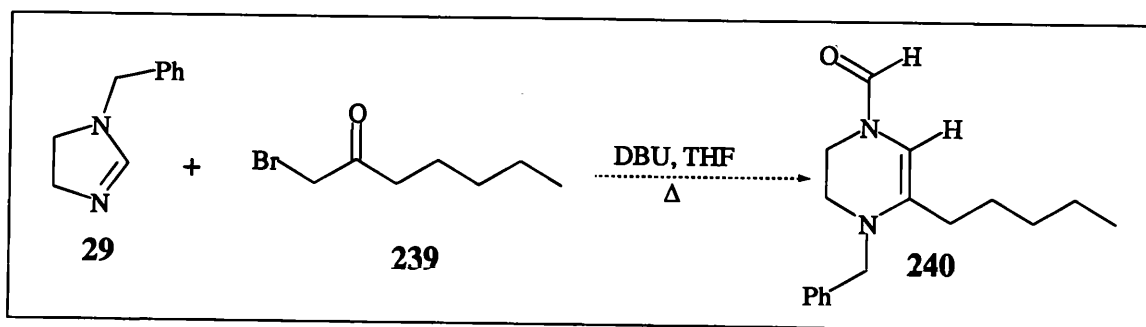
6.98, integrating to one proton in total, are assigned to the 3-CH alkene proton for **232**; that at δ 6.98 is assigned to the *anti* rotamer because of the proximity of the adjacent deshielding formyl oxygen atom. Indeed, the relative intensities of the signals are consistent with this. Thus, the δ 6.98 signal is the smaller of the two alkene signals, and this corresponds with the δ 3.15/ δ 3.30 pair for the ring CH₂ protons, which is the smaller of the two pairs in this region. Naturally, if the alkene proton in the *anti* rotamer is deshielded, then the ring CH₂ protons are not. Finally the singlets at δ 7.90 and δ 8.27, integrating in total to one proton, can be assigned to the formyl proton NCHO for each rotamer of **232**. The downfield signal corresponds to the *syn* rotamer based upon signal intensities and this is also consistent with the deshielding effect of the alkene functionality. The ¹³C NMR spectrum is consistent with **232** and its signal assignment followed. The signals at δ 159.3 and δ 159.9 are due to the formyl carbon atom NCHO for **232** in each rotamer, the signals at δ 108.6 and δ 112.2 to the alkene carbon atom 3-CH for **232** in each rotamer and the signals at δ 143 and δ 147 due to the C-2 in each rotamer. In addition, high-resolution mass spectrometry showed MH^{•+} 323.1268 in agreement with the expected MH^{•+} 323.1270 for **232**.

We rationalize the formation of **232** through initial formation of the corresponding azomethine ylide **231** as shown in Scheme 103. Hydrolysis of this, or its cyclization product **233**, by adventitious moisture will lead to the formation of ketone **237**. However it is formed, the secondary amine moiety of **237** attacks the ketone carbonyl group affords pyrazine **238**, which upon loss of water affords the tetrahydropyrazine **232**.



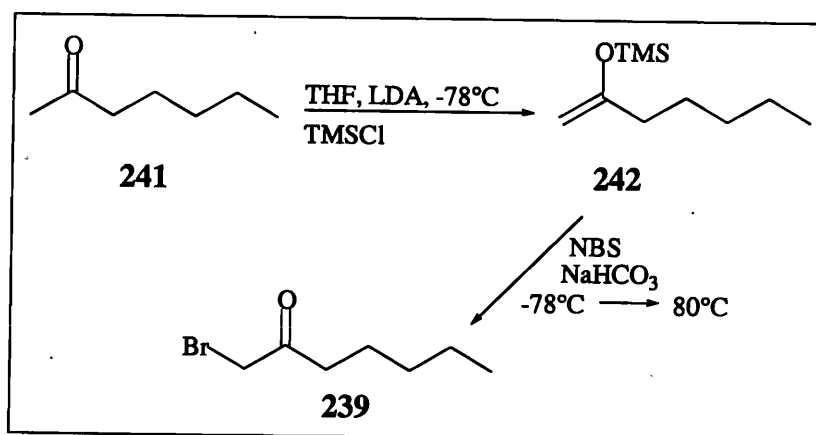
Scheme 103

Clearly, the reaction involving the aryl-substituted bromomethylketone has taken a different pathway to that described for compound **224**. Certainly, the product from reaction of **224** does not have the features consistent with the general framework of **232**. Thus, we decided to investigate the reaction of an alkyl-substituted bromomethylketone in which the alkyl group contained no functionality. We therefore turned our attention to the reaction of 1-bromoheptan-2-one **239** and 1-benzyl-4,5-dihydroimidazole **29** (Scheme 104).



Scheme 104

We prepared 1-bromoheptan-2-one **239** by bromination of commercial heptan-2-one **241** using the α -bromination methodology employed previously. Treatment of heptan-2-one **241** in anhydrous THF at -78°C with a freshly prepared solution of LDA (1.2 equiv.) in anhydrous THF afforded the enolate which was quenched with excess TMSCl to afford the silyl enol ether **242** (Scheme 105). A solution of the latter in anhydrous THF at -78°C was directly treated with solid NaHCO_3 (1.4 equiv.) followed by the addition of NBS (1.3 equiv.) which, after heating at 80°C for 2 hours, afforded 1-bromoheptan-2-one **239** in 41% yield.



Scheme 105

Subsequently, 1-benzyl-4,5-dihydroimidazole **29** in refluxing anhydrous THF under nitrogen was treated with 1-bromoheptan-2-one **239** for 2 h before the addition of DBU and further heating of the resulting solution for 4 h. Upon work-up we isolated a compound that had the ^1H NMR spectrum shown in Figure 25. Clearly this bears no resemblance to the possible structure **240** (see Scheme 104). Indeed, it exhibits all of the features observed for the product from the reaction between **29** and *E*-**224** (see Scheme 98). These are: (1) the diastereotopicity of the methylene benzylic peaks, observable in the ^1H NMR spectrum as two doublets at δ 3.88 and δ 3.37 each integrating to one proton; the triplet signal at δ 3.21 integrating to one proton that has a 5 Hz coupling constant; and (3) the singlet at δ 9.47. Clearly absent in this ^1H NMR spectrum are any alkene signals in the region δ 6.0-7.0, that would correspond to the 3-CH in **240** or some similar structure.

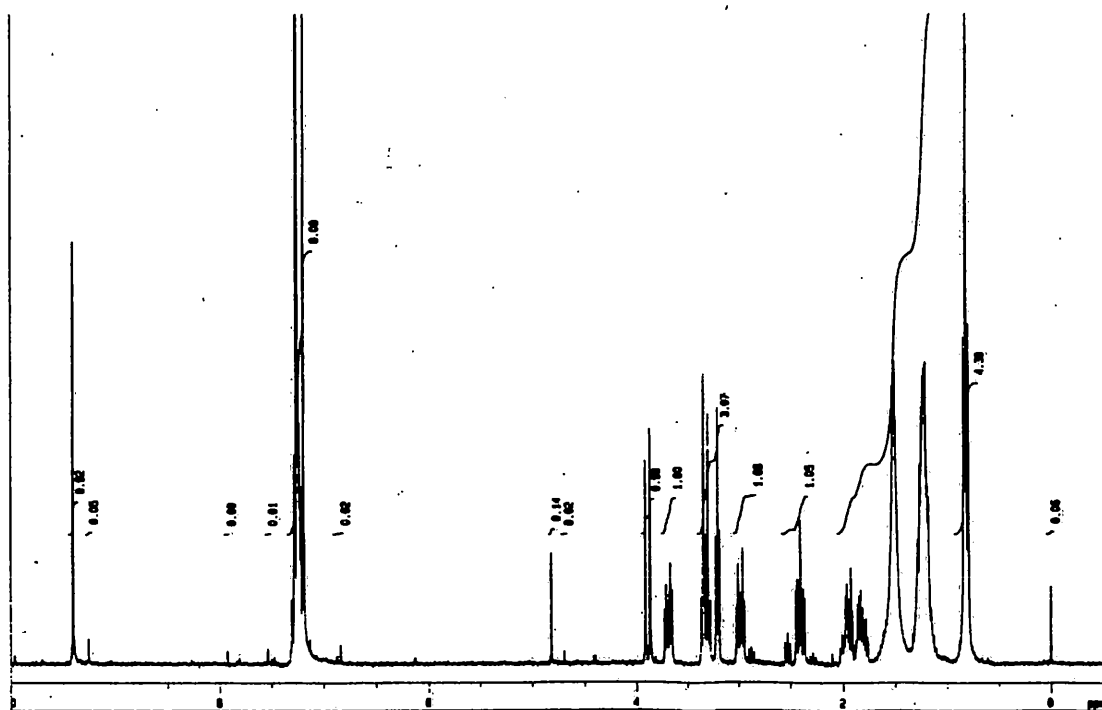
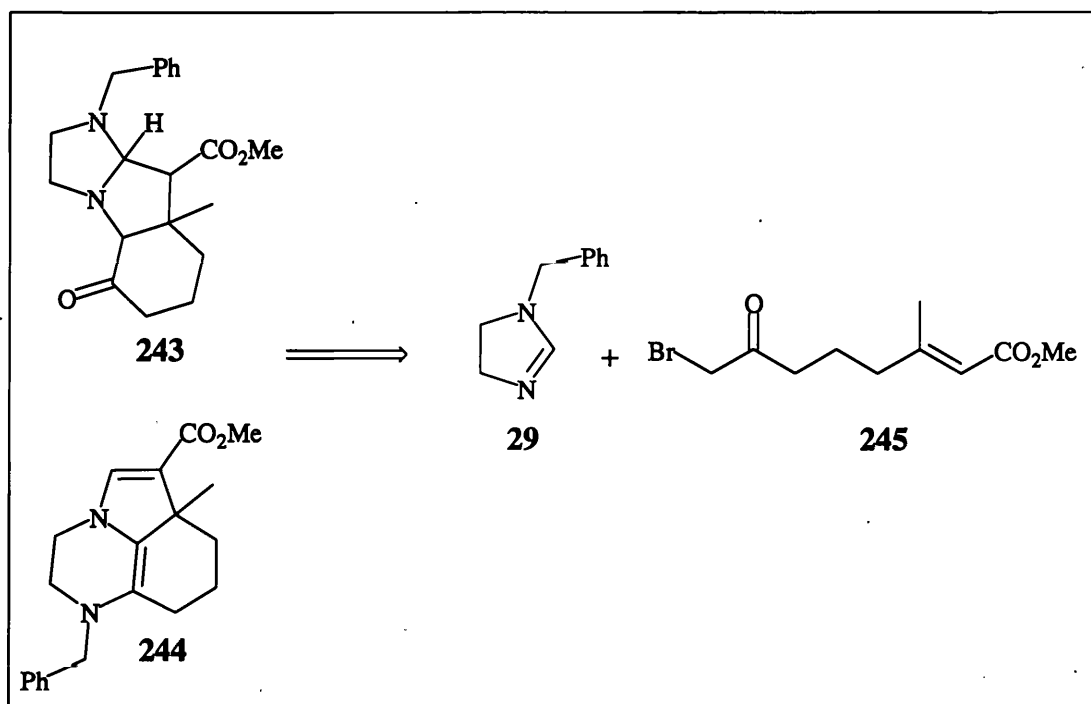


Figure 25: ^1H NMR spectrum for the product isolated from the reaction between **29** and **239**.

Further congruence between the products from the reactions of **29** with **239** and **29** with **224** comes from the ^{13}C NMR spectrum. Once again, the spectrum reveals CH carbon signals at δ 65.5 and δ 162.3 and a quaternary C atom at δ 173.6. The remainder of the signals in the ^{13}C NMR spectrum account for the presence of the benzylic CH_2 carbon atom as well as the CH_2 signals for the carbon atoms belonging to the dihydroimidazole **29** and the aliphatic CH_2 signals for the carbon atoms of 1-bromoheptan-2-one **239**. Indeed all of the carbon atoms in the two starting materials are accounted for by the signals in the ^{13}C NMR spectrum. Low-resolution EI mass spectrometry shows a weak signal at m/z 260, and, in the CI (NH_3), signals at 261 and 289. As before, we have been unable to structurally identify the product obtained in this reaction,[†] although this result confirms that (a) the reaction is typical of bromomethyl alkyl ketones, and (b) the alkene functionality in **224** plays no part in the reaction.

Next we focused our efforts into synthesising a dipolarophile that contained an appropriately positioned methyl group that would block the presumed prototropic shift of the proton in enamine **218**. Our expectation was that this should allow access either to cycloadducts such as **243** or to a ring-opened and recyclized derivative such as **244**. To this end we required the bromomethylketone **245** which bears a methyl group β - to the ester functionality (Scheme 106).

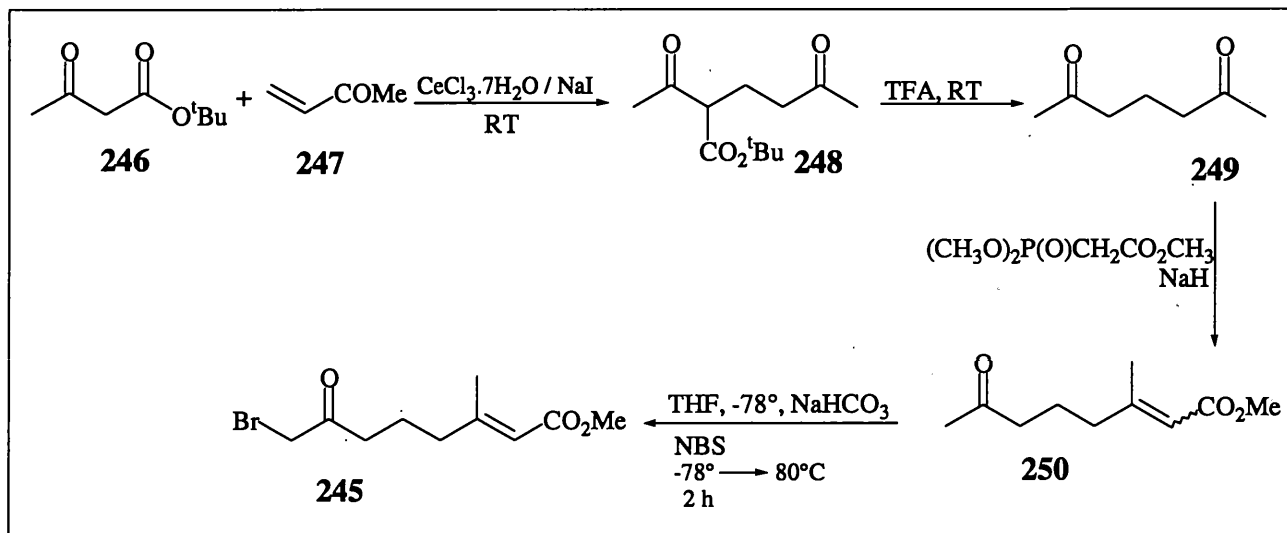
[†] The structure of this compound is described in the addendum on page 235



Scheme 106

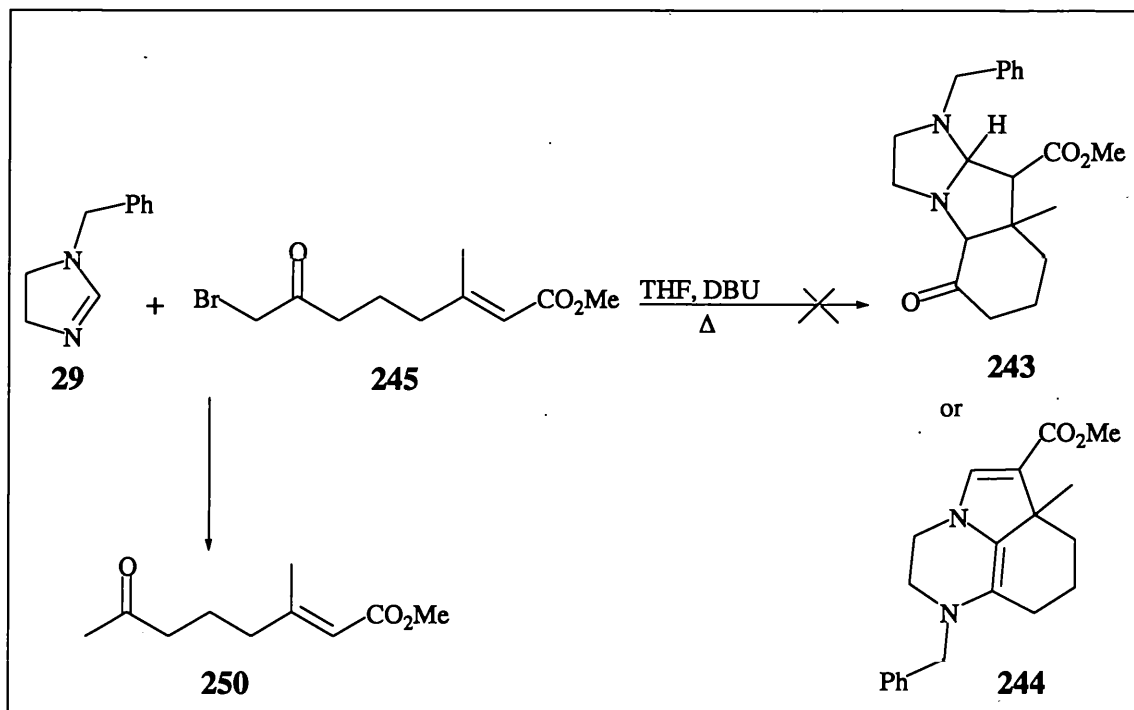
Michael addition of *tert*-butyl acetoacetate **246** and but-3-en-2-one **247** (1.1 equiv.) at RT, catalysed by a mixture of cerium (III) chloride heptahydrate (0.2 equiv.) and sodium iodide (0.1 equiv.), afforded *tert*-butyl 2-acetyl-5-oxohexanoate **248** in 97% yield.¹¹² Acid catalysed ester cleavage-decarboxylation of 2-acetyl-5-oxohexanoate **248** with excess trifluoroacetic acid at RT led to 2,6-heptanedione **249** in 98% yield. Wadsworth-Emmons olefination of diketone **249** with trimethyl phosphonacetate (1.2 equiv.) in the presence of sodium hydride as base (1.2 equiv.) afforded an inseparable 1:1 mixture of methyl *E*- and *Z*-3-methyl-7-oxooct-2-enoate **250** in 40% yield after 10 h at RT. Regioselective bromination of the isomeric mixture **250** proceeded in the usual way. The enolate was formed at -78°C using LDA as base, and this was quenched with excess TMSCl to give the respective intermediate silyl enol ether. The latter, upon reaction with solid NaHCO₃ and

NBS at -78°C and heating of the resulting solution to 80°C for 2 h, afforded the single isolated isomeric methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate **245** in 30% yield. (Scheme 107). Although isolation of *Z*-**245** was expected we were not able to locate this during the purification of the crude mixture.



Scheme 107

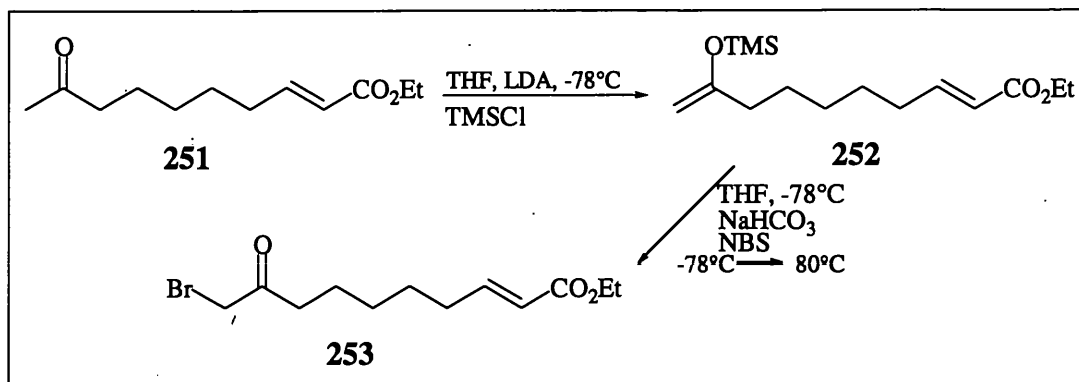
We then investigated whether the 1,3-DC reaction of the dipolarophile **245** with 1-benzyl-4,5-dihydroimidazole **29** would in fact hinder the prototropic shift proposed for **218**. Thus, **29** in anhydrous THF under nitrogen at reflux was treated with methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate **245** and the resulting solution heated at reflux for 2 h before the dropwise addition of DBU. Further heating of the solution was continued for 4 h followed by silica gel column chromatography of the reaction residue. Surprisingly, the major isolated material was the dehalogenated derivative of **245**, *i.e.* methyl *E*-3-methyl-7-oxooct-2-enoate **250** in 20% yield (Scheme 108), contaminated with traces of DBU. Given the results obtained thus far, it is not clear how this arises.



Scheme 108

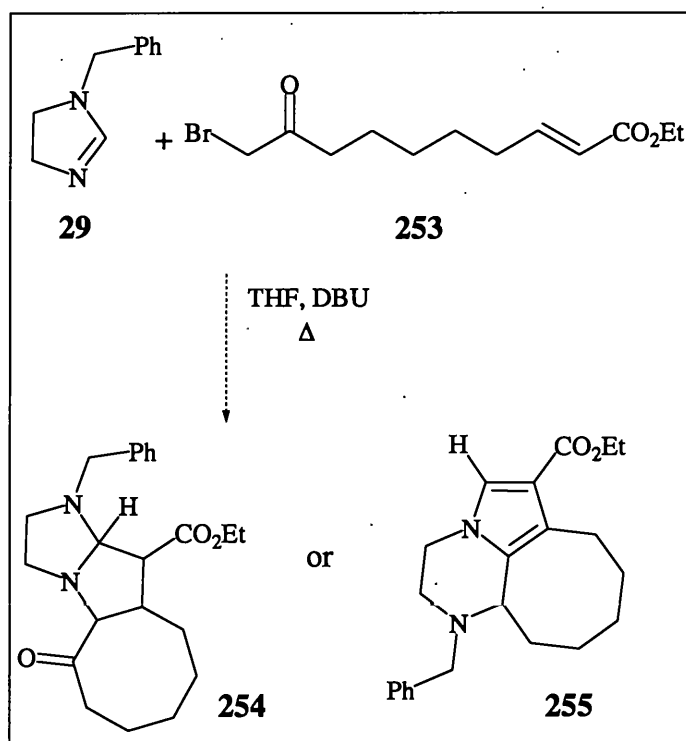
We next decided to investigate the possibility of applying the *intramolecular* cycloaddition reaction to systems that involved longer and shorter alkyl chains between the ketone and alkene functionalities. This has the potential to allow access to larger and smaller carbocyclic derivatives related to the pyrroloquinoxalines **217**.

In the case of a longer chain dipolarophile, we had access to a sample of the ethyl ester **251** of the honeybee “queen substance”.¹¹³ Application of the regioselective α -bromination methodology employed thus far afforded ethyl *E*-10-bromo-9-oxodec-2-enoate **253** in 36% yield (Scheme 109).



Scheme 109

With compound **253** to hand we reacted it with 1-benzyl-4,5-dihydroimidazole **29**, hoping to access tricyclic species such as the primary cycloadduct **254** or the rearranged product **255** (Scheme 110).



Scheme 110

Thus, dihydroimidazole **29** in anhydrous THF under nitrogen and heated at reflux was treated with ethyl *E*-10-bromo-9-oxodec-2-enoate **253** for 2 h before the dropwise addition of DBU over a period of 4 h. Heating was continued for a further 4 h, and after subjection of the residue to silica gel column chromatography, a compound was isolated whose ^1H NMR spectrum is shown in Figure 26. Comparison of this with that in Figure 22 for **217** reveals that the product is not the pyrrolo compound **255**. For example, the unique pyrrolo proton at δ 7.12 in compound **217** is not present in Figure 26. However, the ^1H NMR spectrum is similar to those shown in Figures 23 and 25 that were obtained from the products of the reaction of **29** with *E*-**224** and **239**, respectively. Thus, the ^1H NMR spectrum of the product shows evidence of a chiral centre due to the diastereotopicity of the benzylic methylene protons, which appear as two doublets at δ 3.42 and δ 3.94, each integrating to one proton. Again, we can observe a one-proton singlet at δ 9.47 that may be characteristic of a formyl NCHO signal. Moreover, the triplet signal observed at δ 3.27 integrating to one proton and with a coupling constant of 5.0 Hz is again present (Figure 26). Further, the original alkene protons signals of compound **253** are preserved in the product as revealed by the proton multiplets (both dt) at δ 5.80 and δ 6.94, respectively. Yet again, it is clear that the alkene functionality plays no part in the reaction.

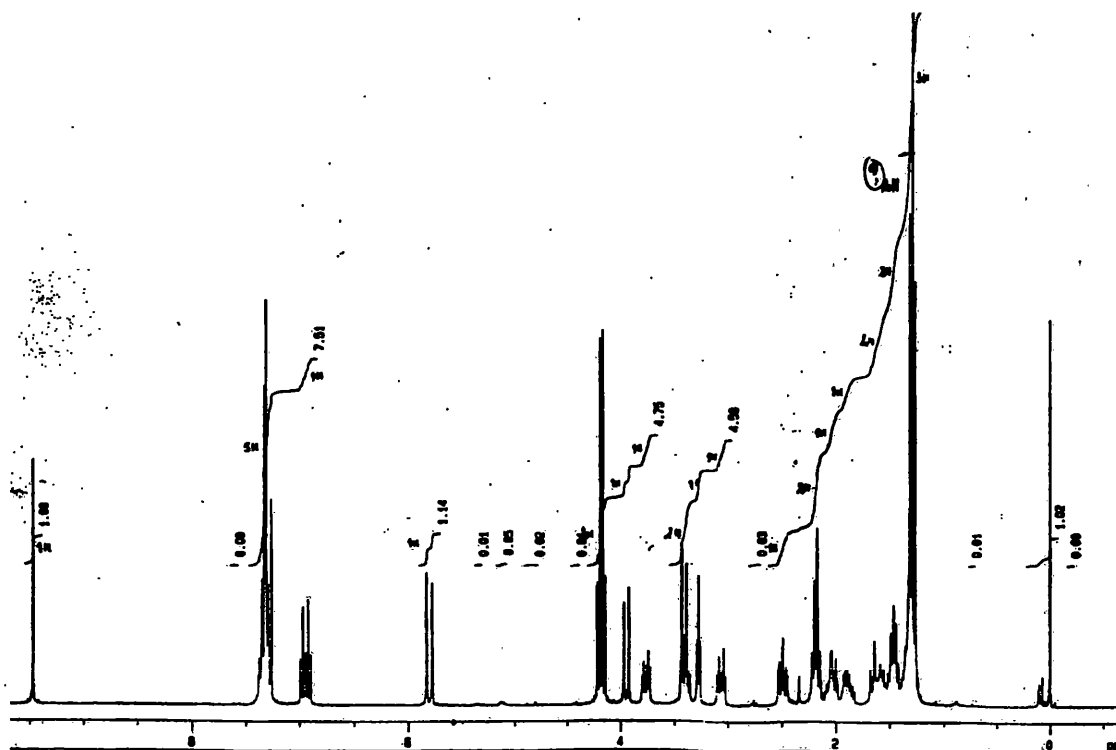


Figure 26: ^1H NMR spectrum of the product isolated from reaction of **29** and **253**.

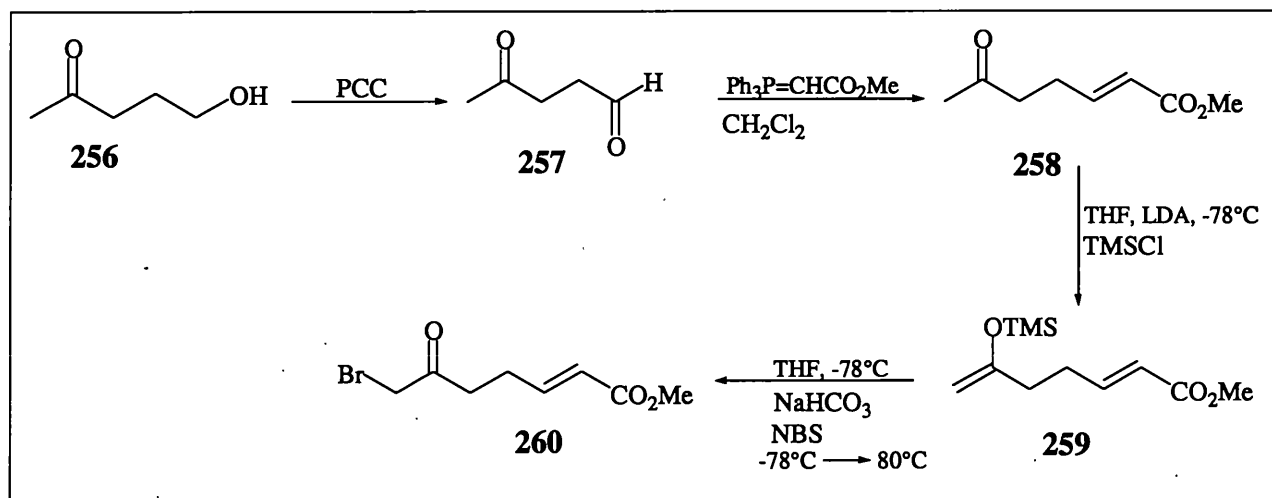
The similarity of the product from this reaction to those of *E*-**224** and **239** is corroborated by the ^{13}C NMR spectrum. This exhibits signals at δ 65.5 and δ 162.4 (CH carbon atoms according to DEPT studies) and δ 173.5 (quaternary carbon atom according to DEPT studies). The remainder of the observed ^{13}C NMR signals was consistent with the carbon atoms of both starting materials **29** and **253**. The presence of the alkene carbon atoms at δ 121.4 (CH) and δ 149.1 (CH) confirmed that the alkene moiety plays no part in the reaction.

Low-resolution EI mass spectrometric analysis, indicated a molecular ion at 386 and CI $(\text{NH}_3) \text{MH}^+$ at m/z 387. Although we were unable to assign the structure of this product,[†] it is obvious that the cycloaddition that was observed for the shorter chain analogue *E*-**196a**

[†] The structure of this compound is described in the addendum on page 235

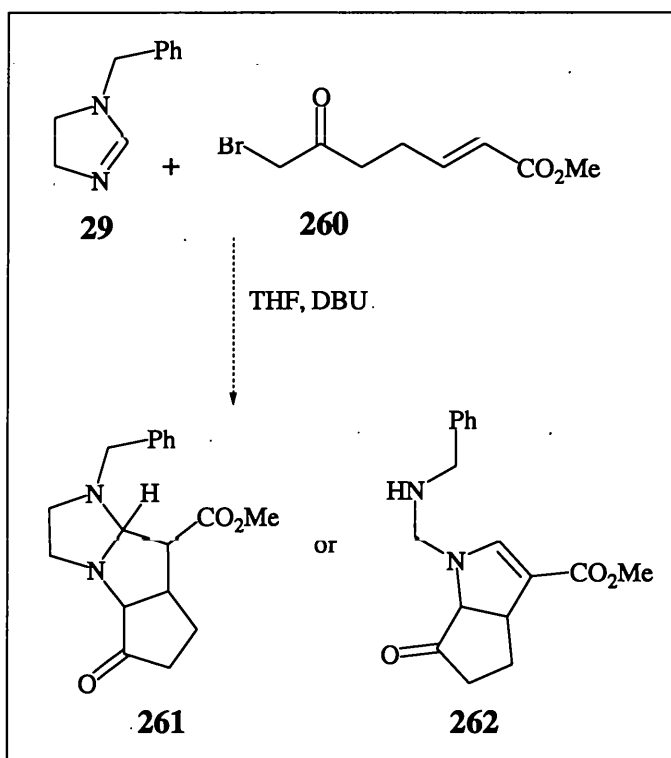
does not occur in this case. Presumably, unfavourable transannular interactions in the transition state leading to the larger ring make its formation disfavoured.

Next, the synthesis of a shorter chain α -haloketone was undertaken. Oxidation of commercial 5-hydroxypentan-2-one **256** with pyridinium chlorochromate (PCC) (1.5 equiv.) afforded, after purification, the desired 4-oxopentanal **257** in rather poor 10% yield. Attempts to improve this low yielding step by employing the alternative Swern oxidation of **256** failed to produce any improvement, yielding products which that could not relate to the expected aldehyde **257** (Scheme 111). However, since starting material **256** was available cheaply the low yielding PCC oxidation step was accepted as adequate. Wittig olefination of aldehyde **257** using methyl (triphenylphosphoranylidene)acetate (1.2 equiv.) afforded, after purification, methyl *E*-6-oxo-hept-2-enoate **258** in 72% yield. Regioselective α -bromination of the latter using the bromination methodology employed for all the dipolarophile precursors synthesised thus far, *i.e.* via the silyl enol ether **259**, afforded, after purification, methyl *E*-7-bromo-6-oxohept-2-enoate **260** in 34% yield (Scheme 111).



Scheme 111

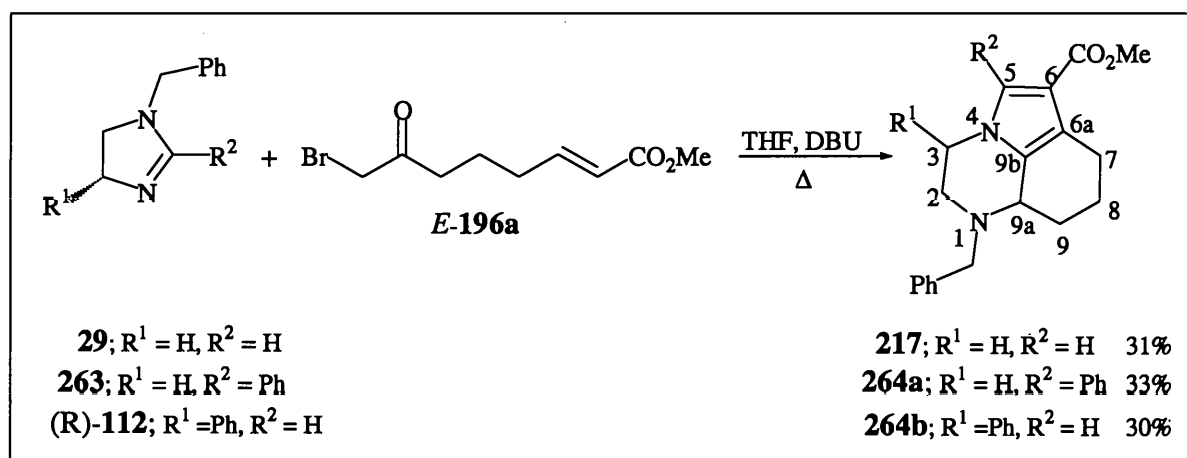
Prior to embarking on the synthesis of **260** and its subsequent reaction with **29**, we constructed a framework molecular model of the expected cycloadduct **261**. Examination of this revealed that, although eliminative ring-opening to give **262** could still occur, closure of the liberated secondary amine onto the ketone carbonyl group and subsequent aromatisation to give a pyrrole ring would be disfavoured due to the angle strain that would ensue. Consequently, we expected that the two likely products of this reaction would be either the dipolar cycloadduct **261** or the ring-opened product **262** (Scheme 112).



Scheme 112

We were surprised to find, however, that after performing the reaction between **29** and **260** under the standard conditions and subjecting the residue to silica gel column chromatography, the major isolated products of the reaction were the unchanged dipolarophile **260** in 30% yield (with some impurities) and 1-benzyl-4,5-dihydroimidazole **29** in 67% yield.

Thus, we returned to the original successful cycloaddition-rearrangement that led to the isolation of methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **217** (Scheme 113). We felt that this presented a valuable and novel synthetic methodology to access heterotricyclic compounds such as **217** derived from primary *intramolecular* 1,3-DC reaction. We decided to further explore this unexpected result and investigate the use of other alkyl esters of the dipolarophile *E*-**196a**, as well as the effect of substitution at C-2 and C-4 of 1-benzyl-4,5-dihydroimidazole **29** on the outcome of the reaction. Since we had already developed an adequate synthetic approach towards the synthesis of dipolarophile *E*-**196a**, we reacted the latter in anhydrous THF under nitrogen and at reflux with 1-benzyl-2-phenyl-4,5-dihydroimidazole **263**.¹¹⁴ The solution was heated for a further 2 h before the dropwise addition of DBU. Further reflux for 4 h followed by purification of the residue afforded, as expected, methyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **264a** in 33% yield. In similar fashion, reaction of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole **112**⁶³ with dipolarophile *E*-**196a** led to methyl (*R*)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **264b** in 30% yield (Scheme 113).



Scheme 113

The structures of both adducts **264a** (Figure 27) and **264b** (Figure 28) were supported by standard spectral data as well as X-ray crystal structure determinations.

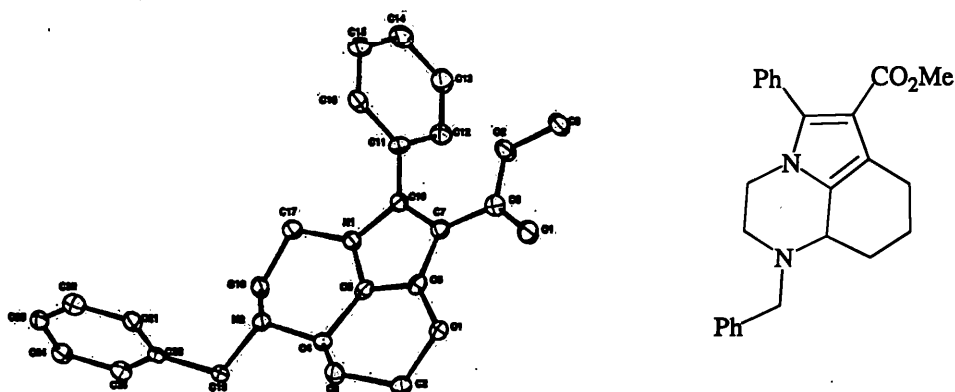


Figure 27: X-Ray crystal structure of pyrrolo[1,2-*de*]quinoxaline **264a**

This latter technique enabled us to determine that the relative stereochemistry for adduct **264b** is as illustrated in Figure 28, *i.e.* that the phenyl 3-substituent and the bridgehead proton at C-9a are located on the same face of the molecule.

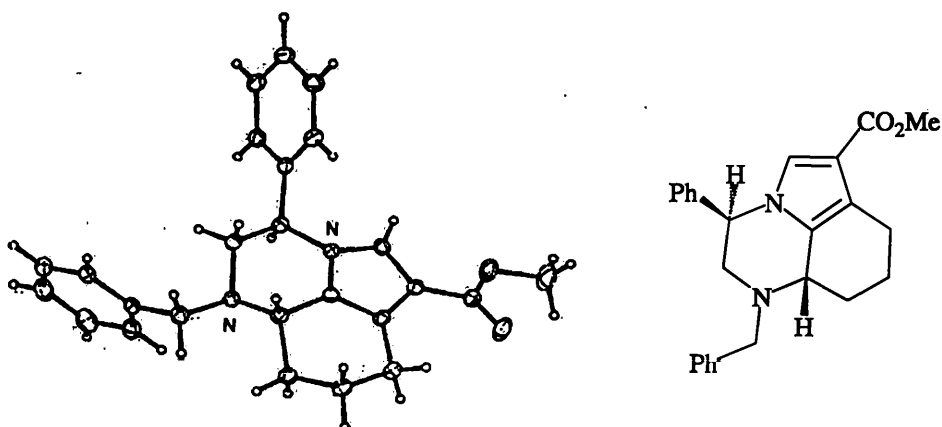
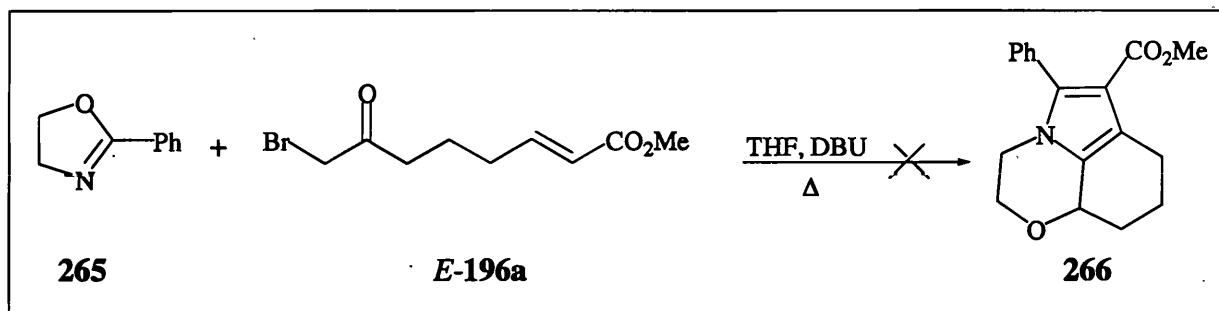


Figure 28: X-Ray crystal structure of pyrrolo[1,2-*de*]quinoxaline **264b**

From these results, it is possible to conclude that the ylide formed from reaction of a 4,5-dihydroimidazole and an α -bromoketone in the presence of base *is* able to undergo *intramolecular* 1,3-dipolar cycloaddition provided that the carbocyclic ring thus formed is six-membered.

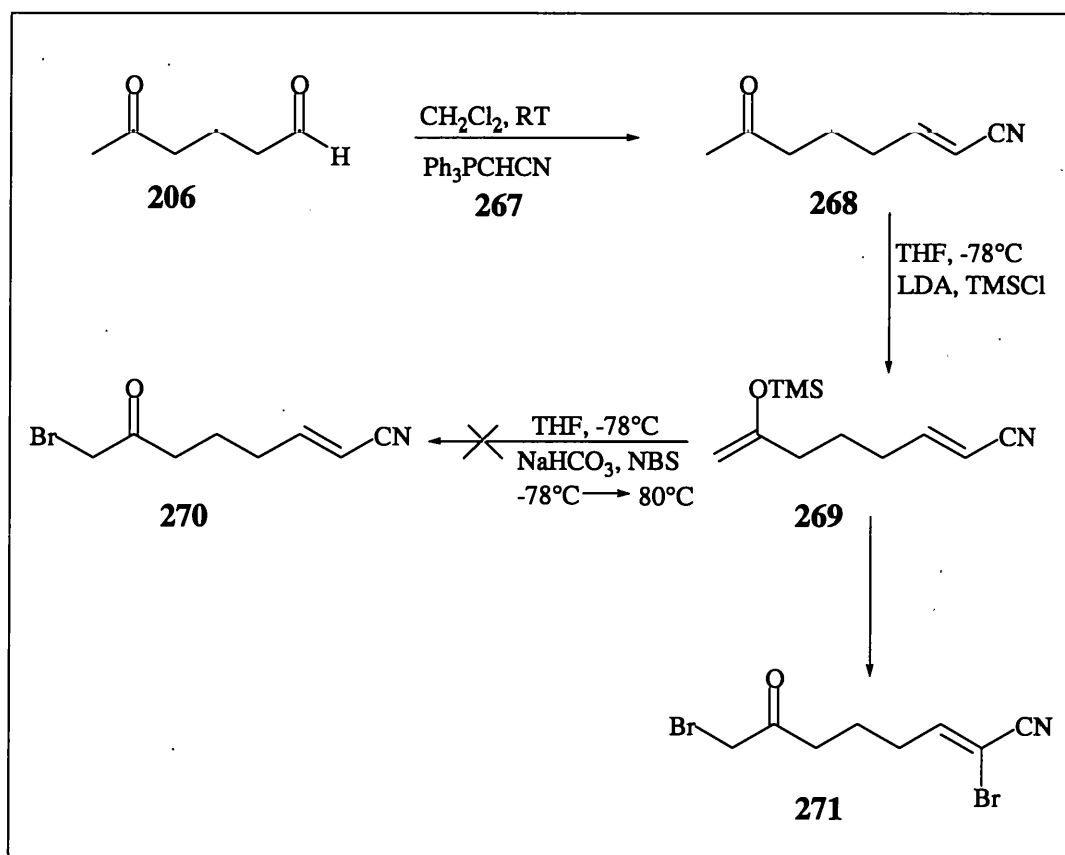
We were interested to see if replacing the 4,5-dihydroimidazole ring by an oxazoline would produce similar results. Thus, commercial 2-phenyl-2-oxazoline **265** was reacted with methyl *E*-8-bromo-7-oxooct-2-enoate **196a** (Scheme 114). However, after subjection of the crude residue to silica gel column chromatography the major compounds recovered were the dipolarophile **196a** in 15% yield (contaminated with DBU traces) and unchanged 2-phenyl-2-oxazoline **265** in 86% yield. The reluctance of oxazolines to undergo N-alkylation has been previously reported by other workers perhaps making these results not so surprising.¹¹⁵



Scheme 114

Similarly, we were interested to discover if a differently functionalised alkene would undergo the 1,3-DC reaction. Thus, we envisaged the use of an α -bromoketone bearing a conjugated nitrile functionality that would hopefully allow access to cyano derivatives of the pyrroloquinoxalines. Wittig olefination of 5-oxohexanal **206** using cyanomethylenetriphenylphosphorane **267** (prepared from chloroacetonitrile and triphenylphosphine)¹⁰⁶ afforded, after purification, the desired *E*-7-oxooct-2-enenitrile **268**

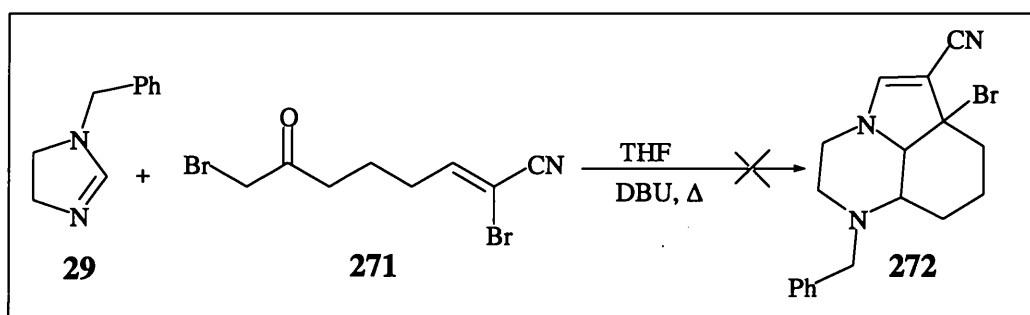
in 53% yield. However, regioselective α -bromination of **268** using the usual protocol, *i.e.* via the corresponding silyl enol ether **269** and addition of NaHCO_3 and NBS did not afford the desired *E*-8-bromo-7-oxooct-2-enenitrile **270**. Analysis of the spectral data for the isolated compound tentatively indicated bis-bromination of the starting material, *i.e.* bromine substitution at the α -carbon of the conjugated nitrile as well as α -bromination at the desired α -position of the ketone had taken place to afford *E*-2,8-dibromo-7-oxooct-2-enenitrile **271** in 12% (Scheme 115).



Scheme 115

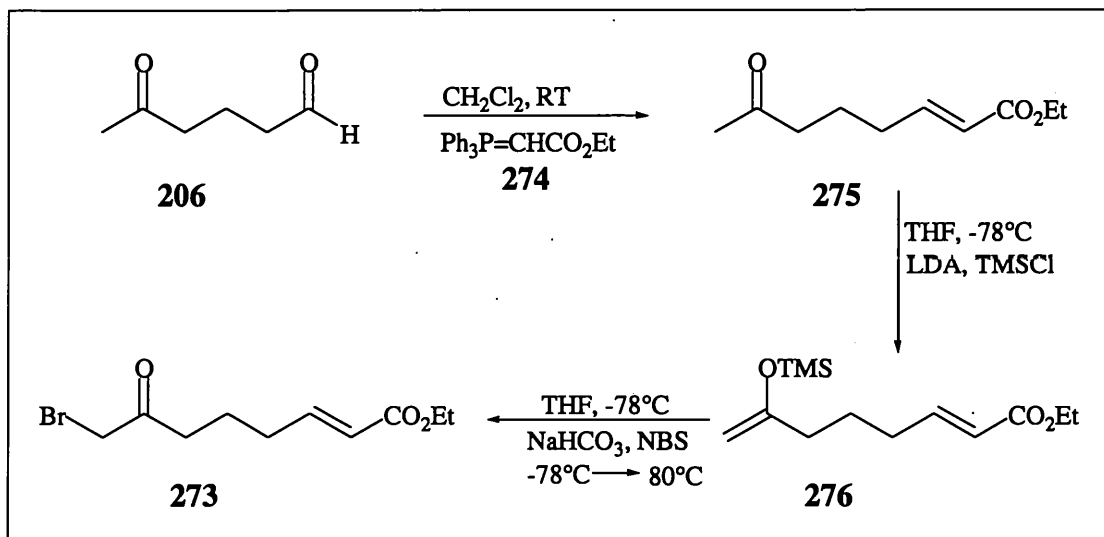
Thus, the ^1H NMR spectrum of the product revealed that the signal (δ 5.40, dt) corresponding to the alkene proton α - to the nitrile group in **268**, was clearly absent. In addition, the signal due to the β -alkene proton (δ 6.78, dt) in **268** is a simple triplet

integrating to one proton. Both observations support the proposal that bromine substitution of double bond α - to the nitrile group has occurred. The ^{13}C NMR spectrum of the product accounted for the correct number of carbons expected for **271** and, in addition, further supported our structural assignment by showing the absence of the peak corresponding to the original α - carbon atom $\text{CH}=\text{CHCN}$ at δ 100.4 and the presence of new alkene signal at δ 121.4 corresponding to the new vinylic carbon atom $\text{CH}=\text{C}(\text{Br})\text{CN}$. Given that **271** contains an α -bromoketone functionality, we attempted a 1,3-DC reaction between the presumed **271** and 1-benzyl-4,5-dihydroimidazole **29**. Unfortunately, after purification, the expected product **272** was not isolated. Only unchanged starting material **29** was isolated in virtually quantitative yield (Scheme 116).



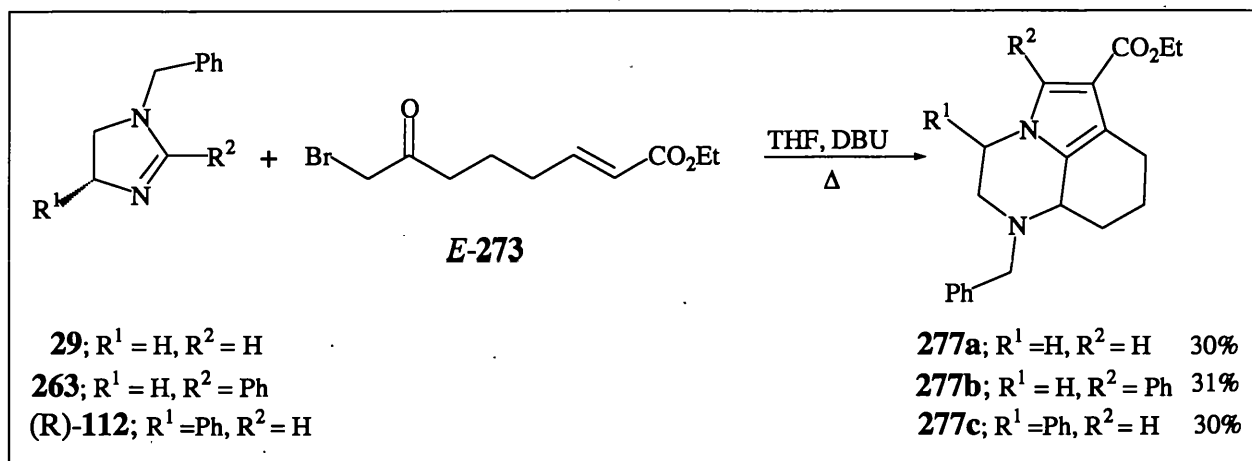
Scheme 116

Further examples of the dipolar cycloaddition-ring opening-recyclization cascade were observed. The ethyl ester variant ethyl *E*-8-bromo-7-oxooct-2-enoate **273** was synthesised from 5-oxohexanal **206** in a similar fashion to methyl *E*-8-bromo-7-oxooct-2-enoate **196a** (see Scheme 92) but employing ethyl (triphenylphosphoranylidene)acetate **274** (freshly prepared from ethyl bromoacetate and triphenylphosphine)¹⁰⁶ in the Wittig olefination step. Regioselective bromination of **275** via the silyl enol ether **276** afforded the ethyl ester **273** in 41% yield (Scheme 117).



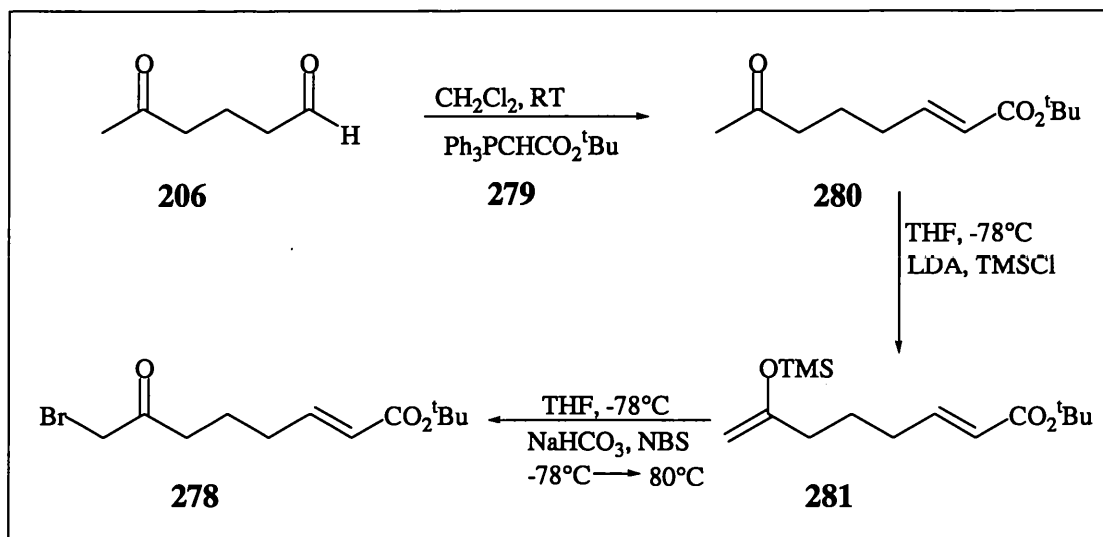
Scheme 117

Treatment of 1-benzyl-4,5-dihydroimidazole **29** with ethyl *E*-8-bromo-7-oxooct-2-enoate **273** in anhydrous THF at reflux and under nitrogen, followed by addition of DBU as usual afforded, after purification, ethyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **277a** in 30% yield. In similar fashion, the reaction of 1-benzyl-2-phenyl-4,5-dihydroimidazole **263** with ethyl *E*-8-bromo-7-oxooct-2-enoate **273** afforded ethyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **277b** in 31% yield, and the reaction of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole **112** with **273** afforded ethyl (*R*)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **277c** in 30% yield (Scheme 118).



Scheme 118

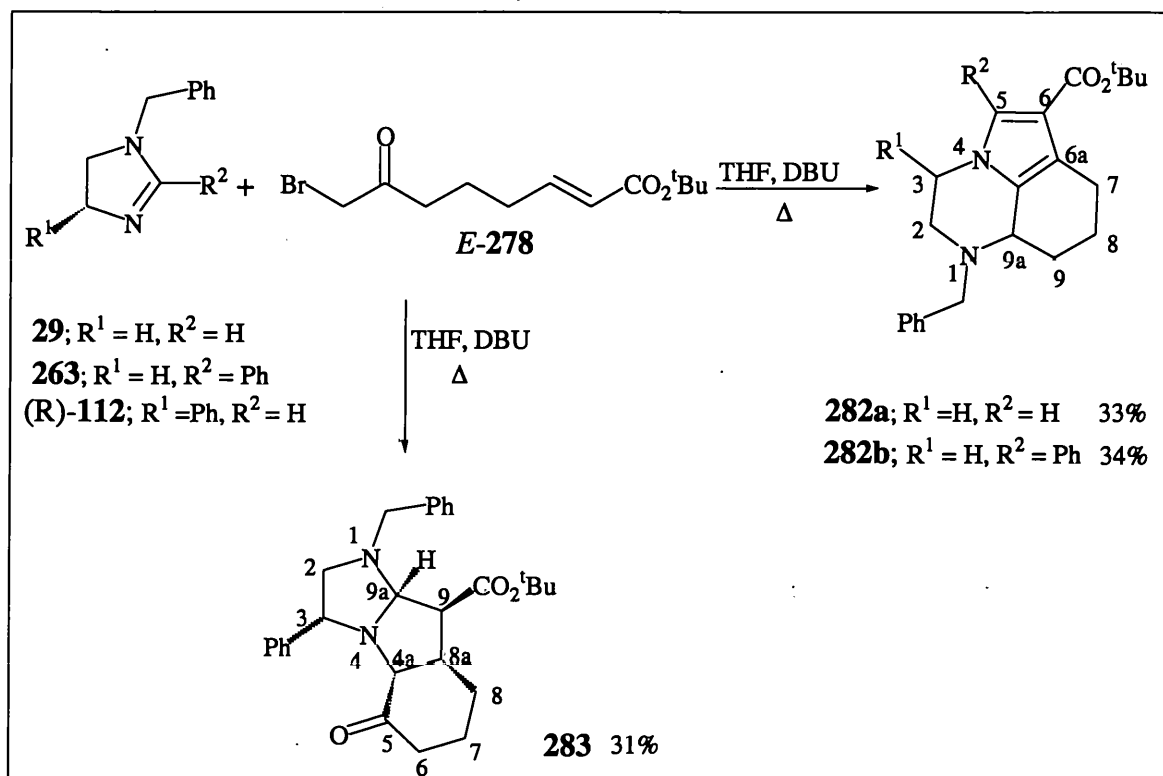
The third ester variant, *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate **278**, was synthesised using the same synthetic methodology described for the synthesis of all the other dipolarophiles. Thus, Wittig olefination of 5-oxohexanal **206** with *tert*-butyl (triphenylphosphoranylidene)acetate **279** (freshly prepared from *tert*-butyl acetate and triphenylphosphine)¹⁰⁶ afforded, after purification, *tert*-butyl *E*-7-oxooct-2-enoate **280** in 58% yield. Regioselective α -bromination proceeded as usual through initial enolate generation and TMSCl quenching to afford the silyl enol ether **281**. Treatment of the latter with solid NaHCO₃ (1.4 equiv.) at -78°C and portionwise addition of NBS (1.3 equiv.) followed by heating afforded *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate **278** in 40% yield (Scheme 119).



Scheme 119

We then reacted the *tert*-butyl ester dipolarophile **278** with 1-benzyl-4,5-dihydroimidazole **29** under the standard cycloaddition conditions to afford, after purification, *tert*-butyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **282a** in 33% yield (Scheme 120). Likewise, changing the dihydroimidazole to 1-benzyl-2-phenyl-4,5-dihydroimidazole **263** afforded *tert*-butyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **282b** in 34% yield. The success of the latter reaction demonstrated the robustness of this dipolar cycloaddition-ring opening-recyclization reaction since the introduction of bulky substituents at both dipole and dipolarophile is tolerated.

Of greater significance, when the procedure was applied to (*R*)-4-phenyldihydroimidazole **112** and the *tert*-butyl ester dipolarophile **278**, for the first time a primary cycloadduct *tert*-butyl (3*R*,4*aR*,8*aS*,9*S*,9*aR*)-1-benzyl-5-oxo-3-phenyldecahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate **283** was isolated (Scheme 120) in 31% yield.



Scheme 120

Indeed, analysis of both ^1H and ^{13}C NMR spectra of **283** did not reveal the usual features of the pyrroloquinoxalines obtained thus far: the characteristic 5-CH pyrrolo proton for compounds such as **282a** at δ 7.12 was clearly absent, as was its corresponding carbon at δ 124.3. In addition, the 9a-CH proton at δ 3.28 (also a common feature in the pyrroloquinoxaline systems thus far obtained) was not observed. Furthermore, the remaining signals for the quaternary carbons of the pyrrole ring in, say **282a**, i.e. δ 113, δ 117 and δ 130 were also absent. The ^1H NMR spectrum of **283** (Figure 29) exhibited the expected main features for such a structure, namely: (1) the diastereotopicity of the methylene benzylic peaks at δ 3.22 and δ 4.11, suggesting the presence of at least one chiral centre; (2) the expected doublet signals⁹⁷ integrating to one proton at δ 3.62 and δ

4.58 corresponding to 4a-CH and 9a-CH; (3) the signal at δ 2.83 integrating to one proton and corresponding to 9-CH in **283** is a triplet due to identically sized coupling to both 9a-CH and 8a-CH. Similarly, in the ^{13}C NMR spectrum the crucial carbonyl carbon atom corresponding to C-5 in **283** is present at δ 210.3.

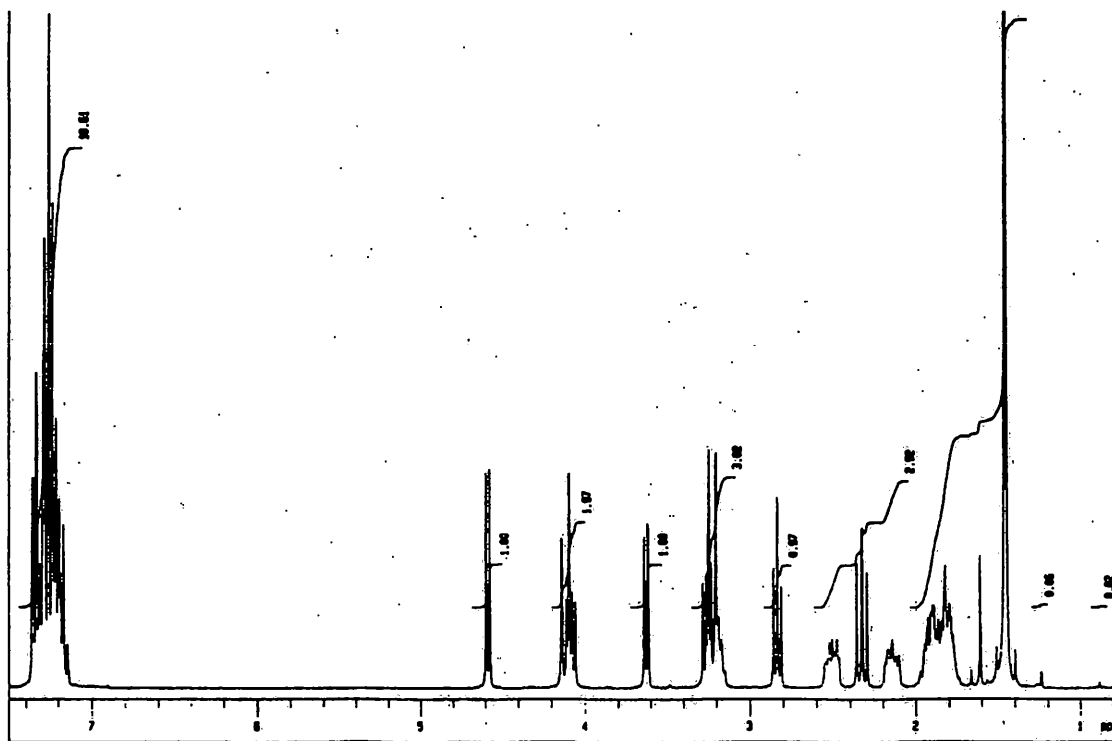


Figure 29: ^1H NMR spectrum of **283**.

An X-ray crystal structure (Figure 30) confirmed the structure and relative stereochemistry of the cycloadduct **283**.

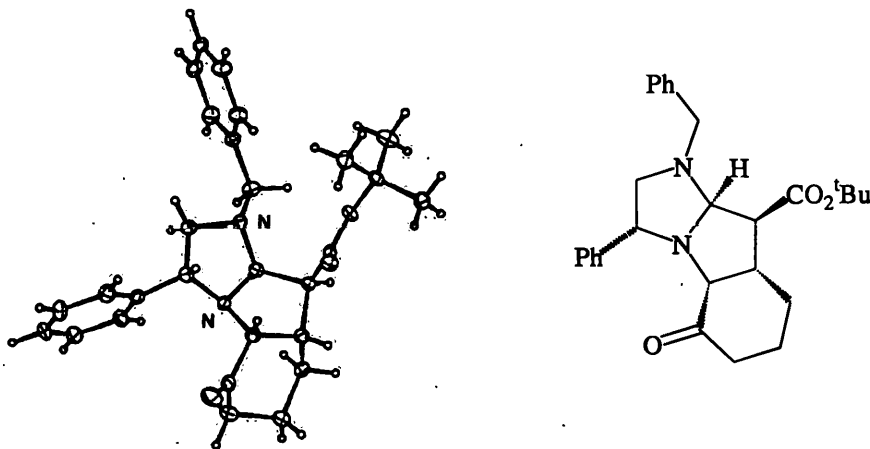


Figure 30: X-Ray crystal structure of cycloadduct **283**.

The stereochemistry of the adduct can be accounted for by the cycloaddition involving an *anti*-dipole adding to a dipolarophile *via* the face *anti* to the 4-phenyl substituent in an *endo*-fashion, as previous researchers in our group have consistently observed with dihydroimidazolium ylides (Figure 30).^{42,85,97} The isolation of **283** supports the suggested sequence for pyrroloquinoxaline **217** formation described in Scheme 94. It appears that the combination of these two particular substituents at the dipole (*R*-phenyl group) and dipolarophile (*tert*-butyl ester) disfavours the eliminative ring-opening process, perhaps for steric reasons.

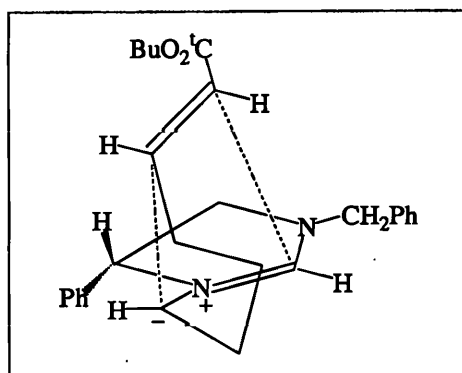
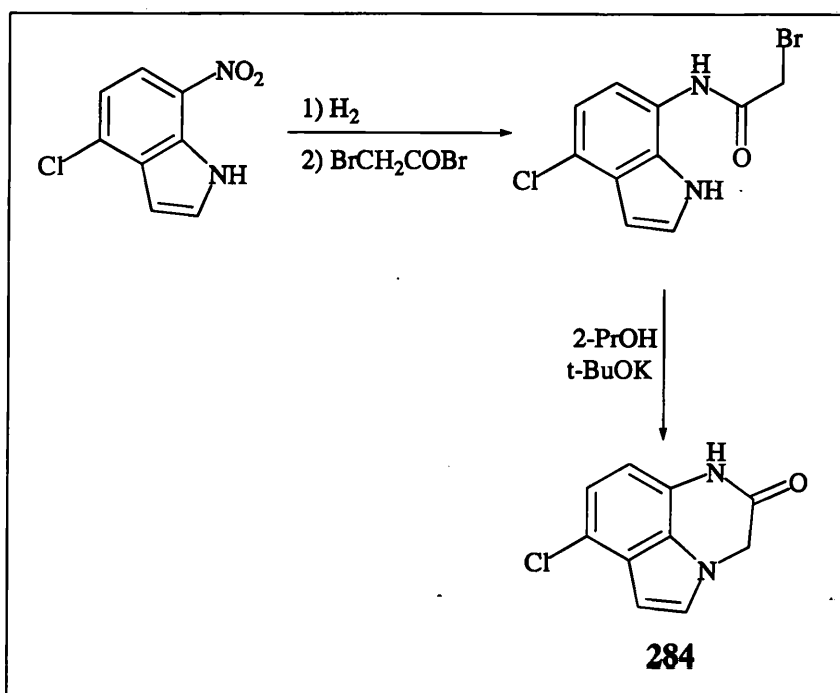


Figure 31: Transition state for intramolecular 1,3-DC reaction of **112** with *E*-**278**.

Summary

Throughout this discussion we have demonstrated that introduction of heteroatom substituent at the C-2 position of 1-benzyl-4,5-dihydroimidazole **29**, followed by N-alkylation of the so-formed heterocycle to form novel azomethine ylides, is, according to our studies, synthetically non-viable thus rendering the application of *intermolecular* 1,3-DC chemistry to these systems not worth exploiting.

However, 4,5-dihydroimidazoles **29**, (*R*)-**112** and **263** undergo N-alkylation and *intramolecular* 1,3-DC cascade reactions with a variety of unsaturated α -bromoketones as dipolarophiles. When both the dihydroimidazole and the dipolarophile contain bulky substituents ((*R*)-**112** and *E*-**278**), the primary imidazo[1,2-*a*]indole cycloadduct **283** is formed. However, in most cases, the initially formed cycloadduct undergoes subsequent eliminative ring-opening, recyclization and tautomerism to form the rarely reported hexahydropyrrolo[1,2,3-*de*]quinoxaline ring system.^{116,117} Previous syntheses have invariably involved annulation of a preformed bicycle (quinoxaline or indole), as exemplified in Scheme 121 for the synthesis of tricycle **284**,^{116f} rendering the *intramolecular* 1,3-DC approach described herein as a novel approach to this system.

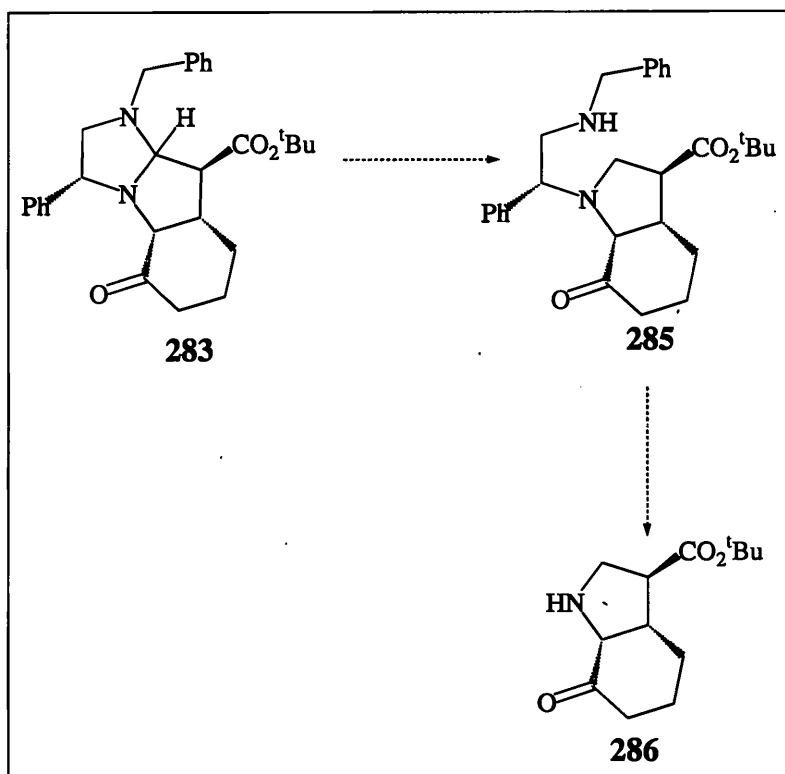


Scheme 121

In addition, these previous reports do not include the hexahydro oxidation level with a pyrrole sub-unit that is afforded by the work described in this thesis.

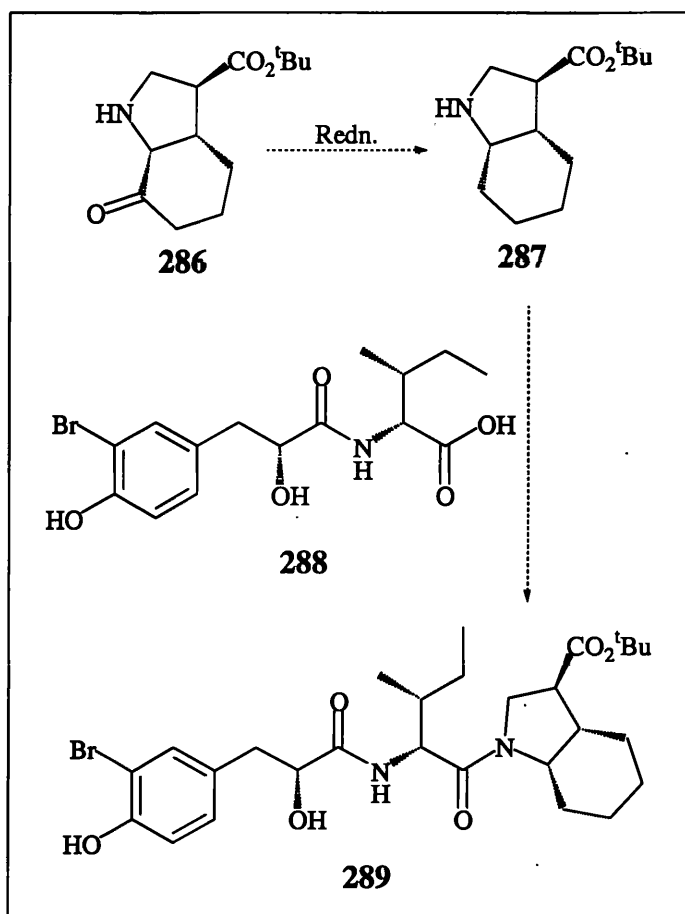
2.3 Future Work

The methodology developed by previous researchers in our group towards template removal⁸⁶ should be applicable to our novel *tert*-butyl 1-benzyl-5-oxo-3-phenyldecahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate **283**. Amino cleavage of **283** by sodium cyanoborohydride would afford the *N*-substituted indole derivative **285**. Debenzylation of **285** by catalytic hydrogenolysis would then furnish the optically active perhydro-indole derivative **286** (Scheme 122).



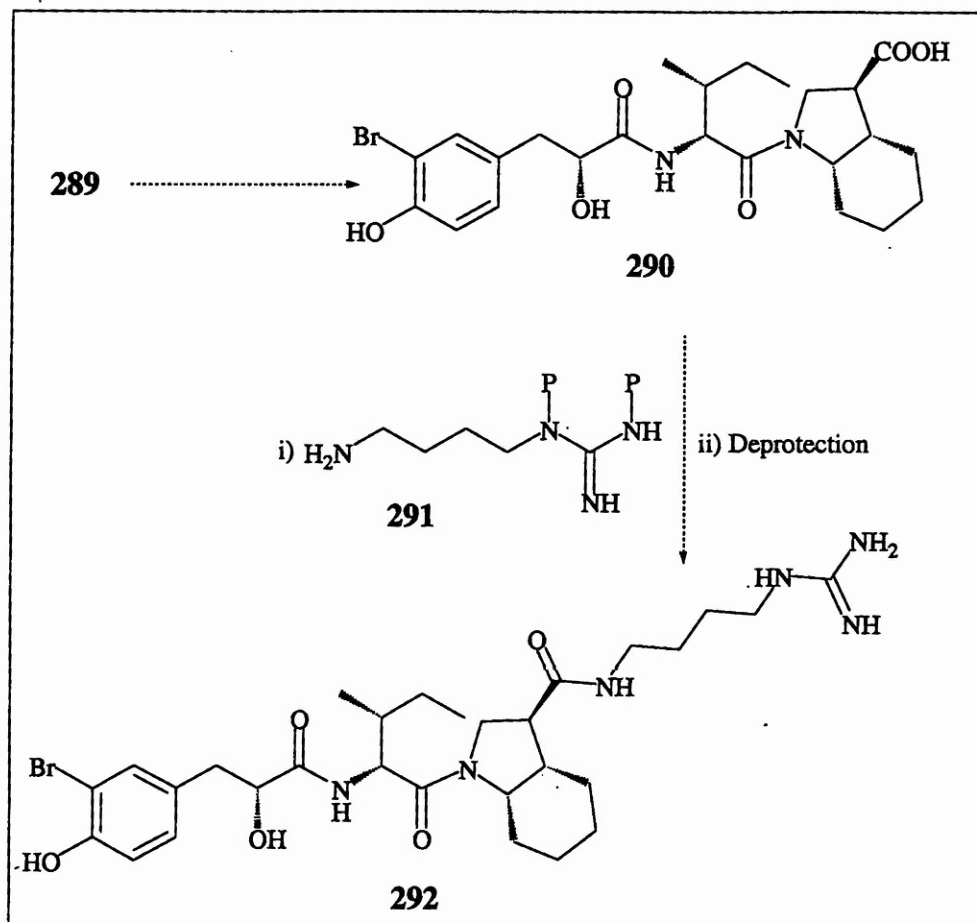
Scheme 122

A more challenging, yet perhaps more interesting, transformation would be the reduction of the carbonyl moiety of **286** to afford **287**, followed by coupling with the amino acid **288** to afford **289** (Scheme 123).



Scheme 123

Hydrolysis of the indole *tert*-butyl ester **289** to the corresponding acid **290** would then set up another potential amino-acid coupling between **290** and the suitably protected amino-acid tether **291** (Scheme 124) to afford, after de-protection, the product **292**, which would constitute an important step *en route* to Aeruginosin 98-C (Figure 21) analogues.



Scheme 124

Chapter 3

Experimental

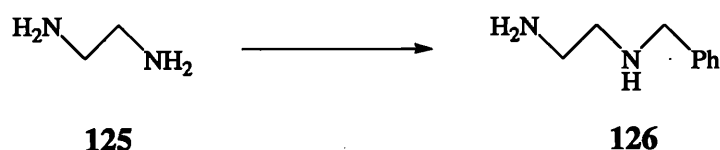
3.0 Experimental

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded in CDCl_3 using either a JEOL EX400 (400MHz and 100MHz, respectively) or a JEOL LA300 spectrometer (300MHz and 75MHz, respectively). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as the internal standard. Multiplicities are: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, sext-sextet, m-multiplet, br-broad signal. Coupling constants (J) are expressed in Hz. Infrared spectra were recorded using a Perkin-Elmer 1710 Fourier Transform Infrared spectrophotometer. Low resolution mass spectra were recorded using a VG Micromass VG-250 mass spectrometer by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) methods, the latter employing a thioglycerol matrix in both positive and negative ion modes. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (University of Wales, Swansea). Elemental analyses were performed by MEDAC Ltd, Brunel Science Centre, Surrey, TW20 0JZ, UK. X-Ray crystallography was performed by the EPSRC X-Ray Crystallographic Service (University of Southampton). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was carried out using Fluka Silica Gel 60 (220-440mesh) (Brockmann 2-3). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV₂₅₄ plates on a plastic backing and visualised by ultraviolet light or aqueous potassium permanganate spray ($\text{KMnO}_4\text{:K}_2\text{CO}_3\text{:water}$, 6:1:100, w/w/v).

All chemicals were purified by distillation or recrystallisation where appropriate. THF, THP, diethyl ether, toluene, ethanol and glyme were dried over sodium or potassium and distilled. DCM and DMSO were dried over sodium or calcium hydride and distilled. Anhydrous reactions were carried out using flamed dried glassware with all transfers performed using oven-dried syringes and needles.

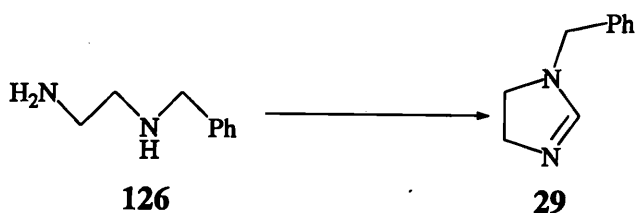
3.1 Intermolecular approach experimental

N-Benzyl-1,2-diaminoethane¹¹⁸



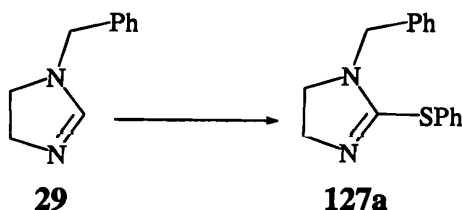
Benzyl chloride (22.89 g; 179.0 mmol) was added dropwise to cooled (0-5°C), stirred 1, 2-diaminoethane (53.94 g; 897.0 mmol) and the resulting solution was heated at reflux for 8 h. After being allowed to cool to room temperature (RT) the solution was then extracted with ether (2 × 10 ml). The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was fractionally distilled under vacuum to afford the title compound as a colourless oil (26.85 g; 62 %): bp 84-86° C / 0.12 mmHg (Lit.,¹¹⁸ 68-75° C / 0.07 mmHg); δ_{H} (400MHz) 1.38 (s, 3H, NH₂ and NH), 2.68 (m, 2H, NHCH₂CH₂N), 2.82 (m, 2H, NHCH₂CH₂N), 3.37 (s, 2H, CH₂Ph), 7.20 (m, 5H, Ar-H); δ_{C} (100MHz) 41.7 (CH₂Ph), 51.9 (NH₂CH₂CH₂NH), 53.8 (NH₂CH₂CH₂NH), 126.8, 128.1, 128.3 (3 × Ar-CH), 140.4 (Ar-C).

1-Benzyl-4,5-dihydroimidazole⁴²



N-Benzyl-1,2-diaminoethane (8.00 g; 5.3 mmol), triethyl orthoformate (31.60 g; 210.0 mmol) and *p*-toluenesulphonic acid (0.18 g; 1.0 mmol) were heated together at reflux for 23 h. After cooling the mixture to RT, aqueous sodium hydroxide (5 % w / v; 50 ml) was added and the mixture was extracted with chloroform (2 × 100 ml). The organic phase was dried (MgSO₄) and evaporated under reduced pressure. The residue was fractionally distilled under vacuum to afford the title compound as a colourless amorphous solid (8.48 g; 51 %): b.p. 112-116°C / 0.15 mmHg (lit.,⁴² 120°C / 2.0 mmHg); δ_{H} (400MHz), 3.15 (t, 2H, $J = 9.9$, NCH₂CH₂N), 3.83 (t, 2H, $J = 9.9$, NCH₂CH₂N), 4.29 (s, 2H, CH₂Ph), 7.04 (s, 1H, N=CHN), 7.34 (m, 5H, Ar-H); δ_{C} (100 MHz) 48.1 (CH₂Ph), 51.7 (NCH₂CH₂N), 54.7 (NCH₂CH₂N), 127.6, 127.8, 128.7 (3 × Ar-CH), 136.7 (Ar-C), 157.5 (N=CH-N).

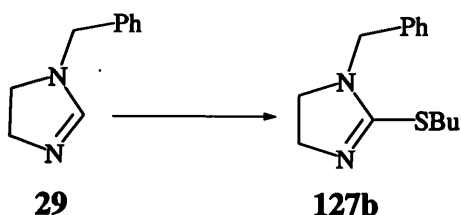
1-Benzyl-2-phenylthio-4,5-dihydroimidazole⁸⁷



According to the literature procedure,⁸⁷ to 1-benzyl-4,5-dihydroimidazole (1.00 g;

6.25 mmol) in dry tetrahydrofuran (THF) (62.5 ml) stirred at -78°C , under an atmosphere of nitrogen, was added *n*-butyl-lithium (2.50 M in hexanes ; 2.5 ml; 7.5 mmol). After 20 min diphenyldisulphide (1.50g; 6.87 mmol) in dry THF (5 ml) was added dropwise and the mixture maintained at -78°C for 2 h. The liquor was allowed to warm to RT and stirred for a further 20 min. The reaction was quenched by the addition of H_2O (2 ml). The organic phase was extracted with ether (2×50 ml), dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using isopropylamine / chloroform (1 : 99 v/v) as eluant to afford the title compound as a yellow gum (0.60 g; 36 %): ν_{max} (film) / cm^{-1} 3063, 2957, 2871, 1568, 1189, 1079, 788 and 700; δ_{H} (400MHz) 3.21 (t, 2H, $J = 6.4$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.68 (t, 2H, $J = 6.4$, $\text{NCH}_2\text{CH}_2\text{N}$), 4.32 (s, 2H, CH_2Ph), 7.26 (m, 10H, Ar-*H*); δ_{C} (100MHz) 50.8 (CH_2Ph) 51.7 ($\text{NCH}_2\text{CH}_2\text{N}$), 53.6 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.2, 127.4, 127.8, 128.7, 128.8, 129.2 ($6 \times \text{Ar-CH}$), 137.2 and 134.4 (Ar-C), 163.92 (C-SPh); m/z (EI) 268 (M^{++} , 48 %).

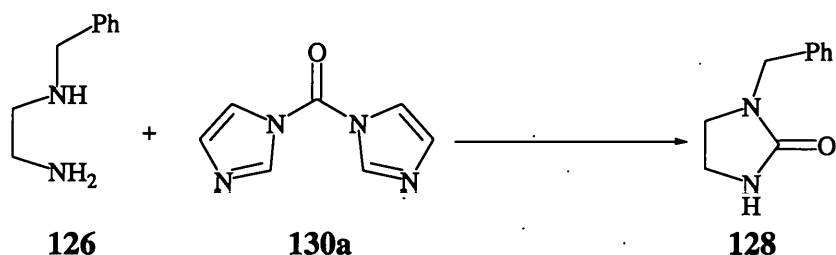
1-Benzyl-2-butylthio-4,5-dihydroimidazole



To 1-benzyl-4,5-dihydroimidazole (0.62 g; 3.87 mmol) in dry THF (38 ml) stirred at -78°C under an atmosphere of nitrogen, was added *n*-butyllithium (2.50 M in hexanes; 1.55 ml; 4.60 mmol). After 20 min dibutyldisulphide (0.76 g; 4.20 mmol) in dry THF (5

ml) was added dropwise and the mixture maintained at -78°C for 2 h. The liquor was allowed to warm up to RT and stirred for a further 20 min. The reaction was quenched by the addition of H_2O (2 ml). The organic phase was extracted with ether (2×50 ml), dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using isopropylamine / chloroform (1 : 99 v/v) as eluant to afford the *title compound* as a yellow gum (0.20 g; 21 %): ν_{max} (film) / cm^{-1} 3063, 2957, 2871, 1568, 1189, 1079, 788; δ_{H} (400MHz) 0.97 (t, 3H, $J = 7.0$, $\text{S}(\text{CH}_2)_3\text{CH}_3$) 1.48 (sext, 2H, $J = 7.0$, $\text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.70 (quin, 2H, $J = 7.0$, $\text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.14 (t, 2H, $J = 6.2$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.23 (t, 2H, $J = 6.2$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.78 (t, 2H, $J = 7.0$, $\text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.29 (s, 2H, CH_2Ph), 7.28 (m, 5H, Ar-H); δ_{C} (100MHz) 13.5 (CH_3) 22.2 ($\text{SCH}_2\text{CH}_2\text{CH}_2$), 30.9 ($\text{SCH}_2\text{CH}_2\text{CH}_2$), 31.5 ($\text{SCH}_2\text{CH}_2\text{CH}_2$), 50.8 (CH_2Ph), 51.1 ($\text{NCH}_2\text{CH}_2\text{N}$), 53.2 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.6, 127.9, 128.4 ($3 \times \text{Ar-CH}$), 137.3 (Ar-C), 164.9 (NC-S); m/z (EI) 248 ($\text{M}^{+\bullet}$, 8%), 215 (14%), 201 (9%), 192 (100%), 178 (6%), 159 (20%), 91 (76%), 89 (9%), 65 (13%), 57 (17%), 44 (31%).

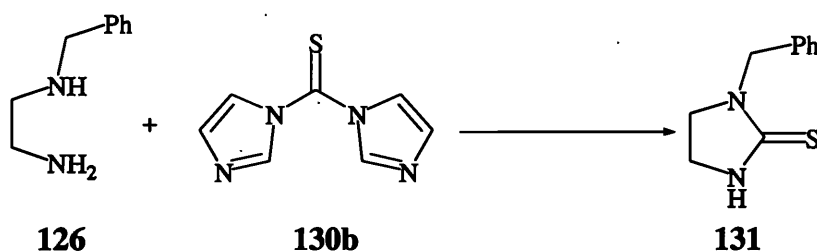
1-Benzyltetrahydroimidazol-2-one



To a solution of N-benzyl-1,2-diaminoethane (5.00 g; 33.0 mmol) in dry THF (200

ml) under nitrogen was added a solution of 1,1'-carbonyldiimidazole (6.48 g; 39.6 mmol) in dry THF (25 ml). The resulting solution was stirred at RT for 18 h. The solvent was removed under reduced pressure and the mixture was washed with dilute hydrochloric acid (2 M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄) and the solvent removed under reduced pressure to afford the title compound as a white crystalline solid (5.79 g; 99%): m.p. 124-127°C (lit.,¹¹⁹ 127°C); ν_{max} (nujol) / cm⁻¹ 1601, 1496, 1467, 1301 and 1116; δ_{H} (400MHz) 3.38 (m, 2H, HNCH₂CH₂N) 3.42 (m, 2H, HNCH₂CH₂N), 4.40 (s, 2H, CH₂Ph), 7.29 (m, 5H, Ar-H); δ_{C} (100MHz) 38.2 (CH₂Ph) 44.5 (NCH₂CH₂N), 47.7 (NCH₂CH₂N), 127.5, 128.1, 128.6 (3 × Ar-CH) 136.9 (Ar-C), 162.8 (NC=O); m/z (EI) 176 (M⁺, 100%), 161 (2%), 147 (35%), 132 (7%), 104 (43%), 99 (28%), 91 (91%), 85 (27%), 77(9%), 65 (21%), 56 (8%); (Found: (EI): M⁺ 176.0941; C₁₀H₁₂N₂O requires M⁺ 176.0949).

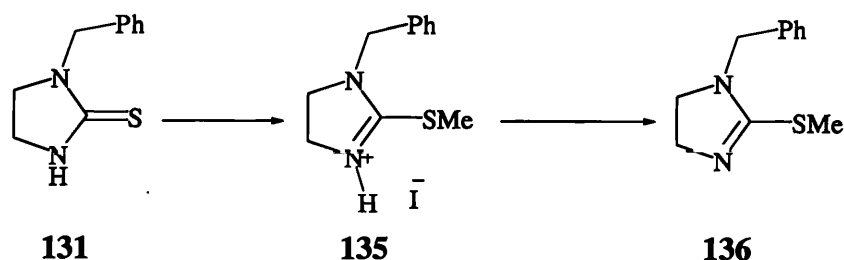
1-Benzyltetrahydroimidazol-2-thione



To a solution of N-benzyl-1,2-diaminoethane (0.50 g; 3.30 mmol) in dry THF (33 ml) under nitrogen was added a solution of 1,1'-thiocarbonyldiimidazole (0.71 g; 3.96 mmol) in dry THF (5 ml). The resulting solution was stirred at RT for 18 h. The solvent was removed under reduced pressure and the mixture washed with dilute hydrochloric acid

(2 M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄) and the solvent removed under reduced pressure to afford the title compound as a white crystalline solid (0.60 g; 94%): m.p. 181-182°C (lit.,¹²⁰ 177-182°C); ν_{max} (nujol) / cm⁻¹ 3401, 2924, 1556, 1377, and 722; δ_{H} (400MHz) 3.60 (s, 4H, NCH₂CH₂NH) 4.84 (s, 2H, CH₂Ph), 7.38 (m, 5H, Ar-H); δ_{C} (100MHz) 41.3 (CH₂Ph) 48.0 (NCH₂CH₂N), 51.0 (NCH₂CH₂N), 127.8, 128.2, 128.7 (3 × Ar-CH), 135.1 (Ar-C), 183.2 (NC=S); m/z (EI) 192 (M^{•+}, 55%), 176 (2%), 131 (10%), 104 (20%), 91 (100%), 89 (7%), 77 (13%), 68 (37%), 65 (32%), 56 (12%); (Found: (FAB): M^{•+} 192.0711; C₁₀H₁₂N₂S requires M^{•+} 192.0721).

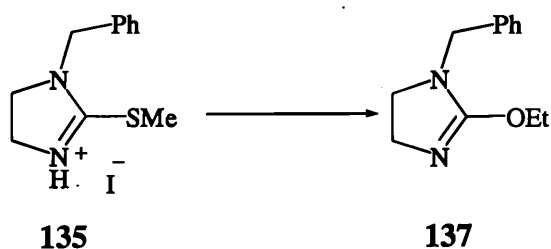
1-Benzyl-2-methylthio-4,5-dihydroimidazole iodide



Methyl iodide (32.0 ml; 50.0 mmol) was added to 1-benzyltetrahydroimidazol-2-thione (2.03 g; 10 mmol) and the mixture was heated at reflux for 16 h under nitrogen. After allowing the mixture to cool to RT the excess MeI was removed under reduced pressure, the residue evaporated twice from dry methanol (2 × 10 ml) to afford the imidazolium salt as a yellow solid (1.89 g, 87%): m.p. 102-105°C; δ_{H} (400MHz) 2.68 (s, 3H, SCH₃), 4.04 (t, 2H, J = 9.2, NCH₂CH₂N), 4.10 (t, 2H, J = 9.2, NCH₂CH₂N), 4.60 (s,

2H, CH₂Ph), 7.33 (m, 5H, Ar-H); δ_c (100MHz) 16.2 (SCH₃), 51.9 (CH₂Ph), 53.3 (NCH₂CH₂N), 53.8 (NCH₂CH₂N), 127.6, 128.3, 128.7 (3 \times Ar-CH), 137.4 (Ar-C), 164.1 (NC-S). A solution of the salt (1.88 g; 5.6 mmol) in dichloromethane (50 ml) was treated with excess K₂CO₃ (7.7 g) and the resulting solution stirred at RT for 1 h. The solution was filtered, extracted with dichloromethane (2 \times 50 ml) and the combined organic phases dried (MgSO₄). The solvent was removed under reduced pressure to afford the *title compound* as a yellow solid (1.61; 86%): m.p. 95-98°C; ν_{\max} (nujol) / cm⁻¹ 3128, 1587, 1563, 1497, 738 and 723; δ_H (400MHz) 2.68 (s, 3H, SCH₃), 3.83 (t, 2H, *J* = 9.2, NCH₂CH₂N), 3.98 (t, 2H, *J* = 9.2, NCH₂CH₂N), 4.37 (s, 2H, CH₂Ph), 7.28 (m, 5H, Ar-H); δ_c (100MHz) 14.6 (SCH₃), 50.89 (CH₂Ph), 51.28 (NCH₂CH₂N), 51.42 (NCH₂CH₂N), 127.8, 128.2, 128.8 (3 \times Ar-CH), 136.2 (Ar-C), 163.8 (NC-S); *m/z* (EI) 206 (M^{•+}, 10%), 191 (17%), 116 (5%), 91 (34%), 28 (100%); (Found: (FAB): M^{•+} 206.0875; C₁₁H₁₄N₂S requires M^{•+} 206.0877).

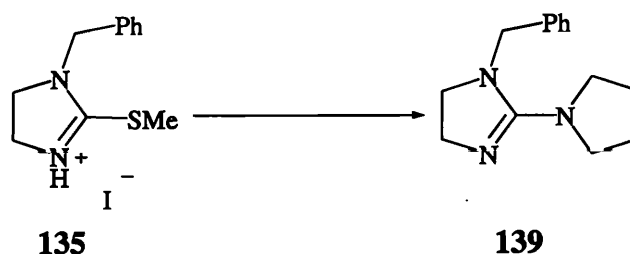
1-Benzyl-2-ethoxy-4,5-dihydroimidazole



A freshly prepared solution of NaOEt (0.38 g; 5.7 mmol) in EtOH (20 ml) was added to 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide (0.46 g; 2.3 mmol) and the resulting solution heated at reflux for 24 h. Water (10 ml) was added to the solution and the

latter extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the *title compound* as a white solid (0.30 g; 66%); m.p. 162-165°C; δ_H (400MHz) 1.20 (t, 3H, $J = 5.2$, OCH₂CH₃) 3.15 (t, 2H, $J = 6.6$, NCH₂CH₂N), 3.32 (t, 2H, $J = 6.6$, NCH₂CH₂N), 4.14 (s, 2H, CH₂Ph), 4.19 (q, 2H, $J = 5.2$, OCH₂CH₃), 7.14 (m, 5H, Ar-H); δ_C (100MHz) 14.62 (OCH₂CH₃), 38.02 (CH₂Ph), 48.32 (NCH₂CH₂N), 49.75 (NCH₂CH₂N), 65.11 (OCH₂CH₃), 127.3, 128.1, 128.6 (3 × Ar-CH), 137.6 (Ar-C), 164.0 (NC-OEt); m/z (EI) 204 (M^{•+}, 18%), 176 (71%), 159 (4%), 91 (100%), 77 (5%), 85 (24%), 65 (19%), 56 (11%); (Found: (FAB): M^{•+} 204.1264; C₁₂H₁₆N₂O requires M^{•+} 204.1262).

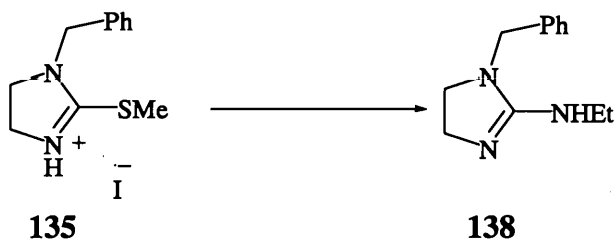
1-Benzyl-2-(pyrrolidin-1-yl)-4,5-dihydro-2-imidazole



A solution of 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide (0.42 g; 2.0 mmol) in dry THF (20 ml) was taken to reflux. At that point pyrrolidine (0.20 ml; 2.0 mmol) was added to the refluxing solution and the heating continued for 20 h. The solution was then allowed to cool to RT, washed with 0.1 M NaOH solution (2 × 10 ml) and extracted with diethyl ether (2 × 50 ml). The combined organic layers were washed with H₂O and extracted with diethyl ether (2 × 50 ml). The final organic layer was dried

(MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using isopropylamine / chloroform (1 : 99 v/v) as eluant to afford the *title compound* as a yellow liquid (0.22 g; 47%): ν_{\max} (film) / cm⁻¹ 2984, 1487, 1226; δ_{H} (400MHz) 1.89 (m, 4H, NCH₂CH₂CH₂CH₂N), 3.40 (m, 2H, NCH₂CH₂N), 3.42 (m, 4H, NCH₂CH₂CH₂CH₂N), 3.72 (t, 2H, *J* = 6.8, NCH₂CH₂N), 4.34 (s, 2H, CH₂Ph), 7.28 (m, 5H, Ar-H); δ_{C} (100MHz) 25.5 (NCH₂CH₂CH₂CH₂N), 49.4 (NCH₂CH₂CH₂CH₂N), 50.6 (PhCH₂), 52.9 (NCH₂CH₂N), 54.2 (NCH₂CH₂N), 126.9, 127.1, 128.6 (3 × Ar-CH), 138.5 (Ar-C), 164.6 (NC-N); *m/z* (EI) 229 (M^{•+}, 54%), 200 (41%), 186 (36%), 159 (61%), 138 (22%), 125 (37%), 110 (23%), 91 (100%), 82 (36%), 70 (53%), 65 (30%), 55 (55%), 41 (28%), 28 (37%); (Found: (EI): M^{•+} 229.1566; C₁₄H₁₉N₃ requires M^{•+} 229.1578).

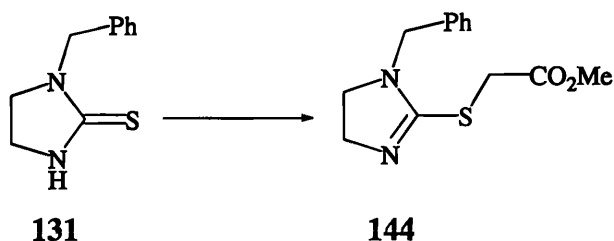
1-Benzyl-2-ethylamino-4,5-dihydroimidazole



A solution of ethylamine in THF (2M; 1.57 ml, 3.15 mmol) was added to a refluxing solution of 1-benzyl-2-methylthio-4,5-dihydroimidazolium iodide (0.45 g, 2.1 mmol) in dry THF (20 ml) and the resulting solution was left at reflux for a further 20 h. The residue was washed with dilute NaOH solution (0.1 M; 50 ml) and extracted with diethyl ether (2 × 50 ml). The organic phase was dried (MgSO₄), filtered and the remaining

solvent evaporated under reduced pressure. The residue was then purified by silica gel column chromatography using isopropylamine / chloroform (1 : 99 v/v) as eluant to yield the *title compound* as a yellow gum (0.40 g, 75%): ν_{\max} (film) / cm^{-1} 3320, 2980, 1440, 1265; δ_{H} (400MHz) 1.40 (t, 3H, $J = 5.7$, NHCH_2CH_3), 3.62 (m, 4H, $\text{NCH}_2\text{CH}_2\text{N}$ and NHCH_2CH_3), 3.76 (t, 2H, $J = 6.9$, $\text{NHCH}_2\text{CH}_2\text{N}$), 4.79 (s, 2H, CH_2Ph), 7.38 (m, 5H, Ar- H); δ_{C} (100MHz) 15.02 (NHCH_2CH_3) 39.27 (NHCH_2CH_3), 47.42 ($\text{NCH}_2\text{CH}_2\text{N}$), 49.83 ($\text{NCH}_2\text{CH}_2\text{N}$), 128.3, 128.6, 129.1 ($3 \times \text{Ar-CH}$), 133.5 (Ar-C), 157.5 (NCNH); (Found: (EI) MH^+ 204.1425; $\text{C}_{12}\text{H}_{17}\text{N}_3$ requires MH^+ 204.1422).

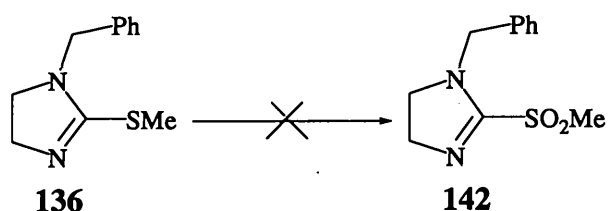
Methyl(1-benzyl-2-methoxycarbonylmethylthio)-4,5-dihydroimidazole



To a solution of 1-benzyltetrahydroimidazol-2-thione (0.30 g; 1.56 mmol) in dry THF (25 ml) under nitrogen was added methyl bromoacetate (0.13 ml; 1.87 mmol). The resulting solution was heated at reflux for 18 h and then allowed to cool to RT. The solvent was evaporated under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (45 : 55 v/v) as eluant to afford the *title compound* as a white solid (0.36 g; 87%): m.p. 111-112°C; ν_{\max} (nujol) / cm^{-1} 2952, 2865, 1740, 1410, 1264; δ_{H} (300MHz) 3.74 (s, 3H, CO_2CH_3), 3.81 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 3.94

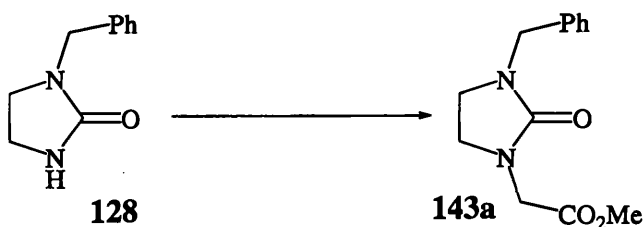
(m, 2H, NCH₂CH₂N), 4.59 (s, 2H, SCH₂CO₂CH₃), 4.70 (s, 2H, CH₂Ph), 7.32 (m, 5H, Ar-H); δ_c (75MHz) 35.6 (CH₂Ph), 44.0 (CO₂CH₃), 49.6 (SCH₂CO₂CH₃), 51.3 (NCH₂CH₂N), 53.6 (NCH₂CH₂N), 128.0, 128.8, 129.3 (3 \times Ar-CH), 132.3 (Ar-C), 168.4 (CO₂CH₃); m/z (EI) 265 (MH⁺, 44%), 192 (100%), 159 (10%), 104 (18%), 91 (50%); (Found: (EI) MH⁺ 265.1014; C₁₃H₁₆N₂O₂S requires MH⁺ 265.1010).

Attempted synthesis of 1-benzyl-2-methylsulfonyl-4,5-dihydroimidazole



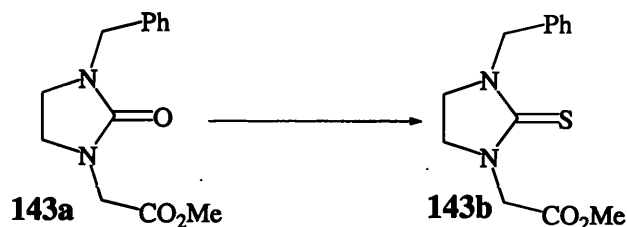
To a solution of Oxone® (3.12 g; 5.07 mmol) in water (25 ml) was added dropwise a solution of 1-benzyl-2-methylthio-4,5-dihydroimidazole **136** (0.30 g; 1.45 mmol) in acetonitrile (10 ml). The resulting solution turned dark after the addition and allowed to stir at RT for 16h. The solvent was evaporated under reduced pressure, the residue extracted with dichloromethane (3 \times 30 ml), dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification of the residue by silica gel column chromatography using isopropylamine / chloroform (1 : 99 v/v) as eluant afforded none of the *title compound*.

1-Benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one



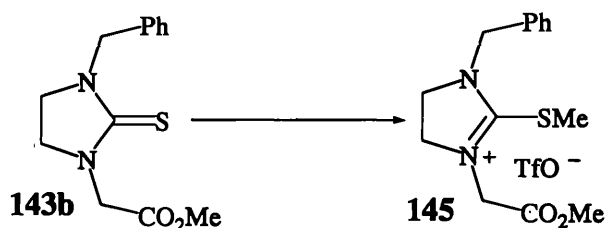
To a solution of 1-benzyl-4,5-dihydroimidazol-2-one (1.03 g; 5.85 mmol) in dry THF (25 ml) under nitrogen at -78°C was added dropwise a solution of *sec*-BuLi (2.5M in hexanes; 7.02 mmol). The mixture was left at -78°C for 10 min and methyl bromoacetate (5.40 ml; 7.02 mmol) was then added dropwise. The mixture was heated at reflux for 24 h and then allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant to afford the *title compound* as colourless oil (0.60 g; 41%): ν_{max} (film) / cm^{-1} 2952, 2872, 1748, 1700, 1400, 1495, 1449, 1361, 1264, 1214, 986, 937, 760, 703; δ_{H} (300MHz) 3.25 (t, 2H, $J = 10.6$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.44 (t, 2H, $J = 10.6$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.75 (s, 3H, CO_2CH_3), 4.03 (s, 2H, $\text{CH}_2\text{CO}_2\text{CH}_3$), 4.40 (s, 2H, CH_2Ph), 7.33 (m, 5H, Ar-H); δ_{C} (75MHz) 42.0 (CH_2Ph), 43.0 (CO_2CH_3), 45.6 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 48.2 ($\text{NCH}_2\text{CH}_2\text{N}$), 52.0 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.4, 128.1, 128.6 ($3 \times \text{Ar-CH}$), 137.0 (Ar-C), 163.0 (NC=O), 170.1 (CO_2CH_3); m/z (EI) 248 ($\text{M}^{+\bullet}$, 12%), 189 (22%), 175 (5%), 92 (8%), 91 (100%), 65 (9%), 42 (9%); (Found: (EI): $\text{M}^{+\bullet}$ 248.1157; $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$ requires $\text{M}^{+\bullet}$ 248.1161).

1-Benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione



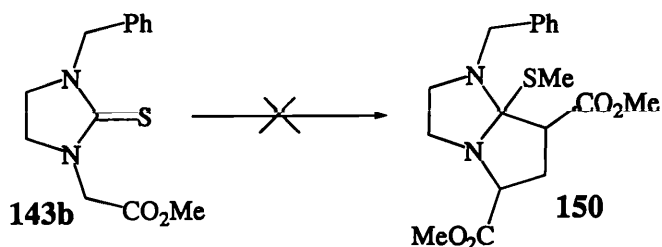
To a solution of the 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (0.20 g; 0.75 mmol) in dry *ortho*-xylene (30 ml) was added portion wise Lawesson's Reagent ([2,4-bis(4-methoxyphenyl)]-1,3-dithia-2,4-diphosphetane-2,4-disulfide) (0.30 g; 0.75 mmol). The mixture was taken to reflux for 26 h after which time it was allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant to yield the *title compound* as yellow gum (0.14 g; 66%): ν_{\max} (film) / cm^{-1} 2950, 2874, 1742, 1404, 1497, 1449, 1266, 1211, 983, 762; δ_{H} (300MHz) 3.45 (t, 2H, $J = 10.7$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.64 (t, 2H, $J = 10.7$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.77 (s, 3H, CO_2CH_3), 4.44 (s, 2H, $\text{CH}_2\text{CO}_2\text{CH}_3$), 4.91 (s, 2H, CH_2Ph); δ_{C} (75MHz) 45.6 (CH_2Ph), 46.4 (CO_2CH_3), 48.8 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 51.8 ($\text{NCH}_2\text{CH}_2\text{N}$), 52.2 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.7, 128.1, 128.7 ($3 \times \text{Ar-CH}$), 138.2 (Ar-C), 170.0 (CO_2CH_3), 183.6 (NC=S); m/z (EI) 264 (M^{+} , 40%), 205 (22%), 191 (8%), 141 (10%), 102 (8%), 91 (100%), 72 (16%), 65 (14%), 42 (13%), 28 (27%); (Found: (EI): M^{+} 264.0931; $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ requires M^{+} 264.0932).

**1-Benzyl-3-methoxycarbonylmethyl-2-methylthio-4,5-dihydroimidazolium
trifluoromethanesulfonate**



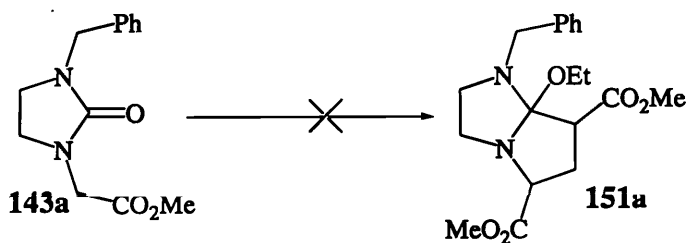
To a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione (0.30 g; 1.10 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere, was added neat methyl trifluoromethanesulfonate (0.15 ml; 1.36 mmol) and the solution allowed to stir at RT for 1 h. The solvent was removed under reduced pressure to yield the *title* compound as a yellow gum (0.46 g; 97%); δ_{H} (300MHz) 2.78 (s, 3H, SCH₃), 3.71 (t, 2H, $J = 10.4$, NCH₂CH₂N), 3.82 (t, 2H, $J = 10.4$, NCH₂CH₂N), 3.75 (s, 3H, CO₂CH₃), 4.54 (s, 2H, CH₂CO₂CH₃), 5.03 (s, 2H, CH₂Ph); δ_{C} (75MHz) 17.2 (SCH₃), 47.1 (CH₂Ph), 46.9 (CO₂CH₃), 49.2 (CH₂CO₂CH₃), 53.1 (NCH₂CH₂N), 53.6 (NCH₂CH₂N), 127.8, 128.4, 128.8 (3 \times Ar-CH), 140.2 (Ar-C), 171.7 (CO₂CH₃), 185.1 (NC=S).

Attempted synthesis of dimethyl 1-benzyl-7a-methylthiohexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-5,7-dicarboxylate



Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.25ml; 2.22 mmol) to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-thione (0.49 g; 1.85 mmol) in dry THF (20 ml) under nitrogen. The solution was stirred at RT for 1 h before methyl acrylate (0.50 ml; 5.55 mmol) was added and the resulting mixture heated to reflux. DBU (1,8-diazabicyclo [5.4.0]undec-7-ene) (0.32 ml; 2.22 mmol) was then added dropwise over a period of 4 h and heating was continued for a further 4 h. The solvent was evaporated under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (4: 6 v/v) as eluant but none of the *title compound* was isolated.

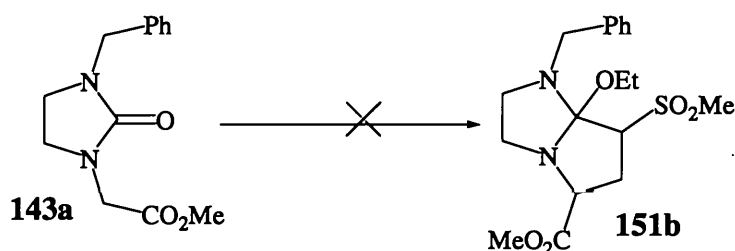
Attempted synthesis of dimethyl 1-benzyl-7a-ethoxyhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-5,7-dicarboxylate



Via a syringe was added dropwise triethyloxonium tetrafluoroborate (1.0M solution

in dichloromethane; 0.96 ml; 0.96 mmol) to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (0.20 g; 0.8 mmol) in dry THF (20 ml) under nitrogen. The solution was stirred at RT for 4 h before methyl acrylate (0.22 ml; 2.4 mmol) was added and the resulting mixture heated to reflux. DBU (0.14 ml; 0.96 mmol) was then added dropwise over a period of 4 h and heating was continued for a further 4 h. The mixture was then allowed to cool to RT, the solvent removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant but none of the *title compound* was isolated.

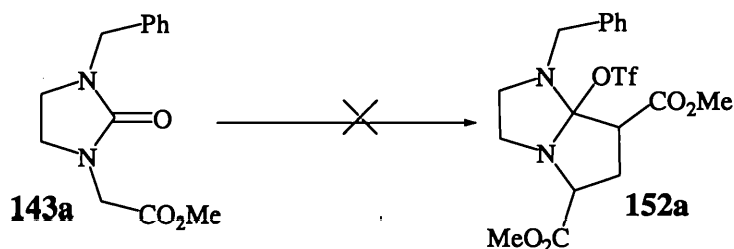
Attempted synthesis of methyl 1-benzyl-7a-ethoxyhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-5-methoxycarbonyl-7-sulfonyl



Via a syringe was added dropwise triethyloxonium tetrafluoroborate (1.0 M solution in dichloromethane; 2.30 ml; 2.23 mmol) to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (0.47 g; 1.89 mmol) in dry THF (20 ml) under nitrogen. The solution was stirred at RT for 4 h before methyl vinyl sulfone (0.49 ml; 5.67 mmol) was added and the resulting mixture heated to reflux. DBU (0.34 ml; 2.30 mmol) was then added dropwise over a period of 4 h and heating was continued for a

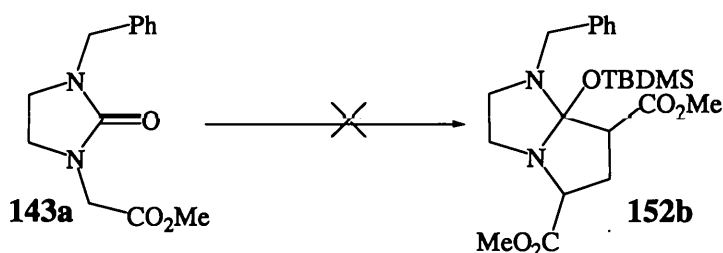
further 4 h. The mixture was then allowed to cool to RT, the solvent removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant but none of the *title compound* was isolated.

Attempted synthesis of dimethyl 1-benzyl-7a-trifluoromethanesulfonyloxyhexahydro-1H-pyrrolo[1,2-*a*]imidazole-5,7-dicarboxylate



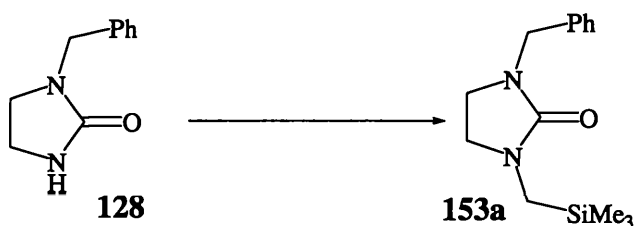
Via a syringe added dropwise trifluoromethane sulfonic anhydride (0.25 ml; 1.50 mmol) to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (0.31 g; 1.25 mmol) in dry THF (20 ml) under nitrogen. The solution was stirred at RT for 2 h before methyl acrylate (0.33 ml; 3.75 mmol) was added and the resulting mixture heated to reflux. DBU (0.22 ml; 1.50 mmol) was added dropwise over a period of 4 h and heating was continued for a further 4 h. The mixture was allowed to cool to RT, the solvent removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant but none of the *title compound* was isolated.

Attempted synthesis of dimethyl 1-benzyl-5,7-bis(methoxycarbonyl)-7a-*tert*-butyldimethylsilyloxyhexahydro-1*H*-pyrrolo[1,2-*a*]-imidazole-5,7-dicarboxylate



Via a syringe was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.11 ml; 0.48 mmol) to a solution of 1-benzyl-3-methoxycarbonylmethyltetrahydroimidazol-2-one (0.10 g; 0.40 mmol) in dry THF (20 ml) under nitrogen. The solution was stirred at RT for 2 h before methyl acrylate (0.10 ml; 1.20 mmol) was added and the resulting mixture heated to reflux. DBU (0.07 ml; 0.48mmol) was added dropwise over a period of 4 h and heating was continued for a further 4 h. The mixture was allowed to cool to RT, the solvent removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant but none of the *title compound* was isolated.

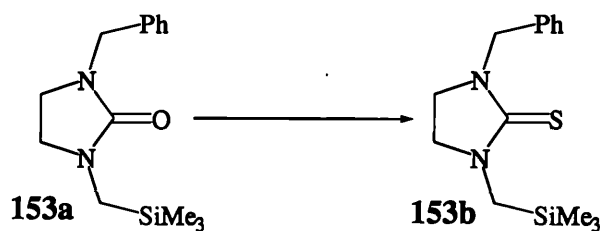
1-Benzyl-3-trimethylsilylmethyl-4,5-tetrahydroimidazol-2-one



To a suspension of NaH (0.19 g; 8.29 mmol) in dry DMSO (25 ml) was added

dropwise a solution of 1-benzyl-4,5-dihydroimidazol-2-one (1.46 g; 8.29 mmol) in dry DMSO (25 ml) at RT. The mixture was stirred for 30 min and then chlorotrimethylsilane (2.24 ml; 12.43 mmol) was added. The resulting mixture was stirred at RT for 10 h. Unreacted NaH residue was filtered off and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant to afford the *title compound* as colourless oil (0.99 g; 45%): ν_{\max} (film) / cm^{-1} 3030, 2952, 2860, 1696, 1444, 1359, 1251, 856, 756; δ_{H} (300MHz) 0.31 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 2.54 (s, 2H, $\text{CH}_2\text{Si}(\text{CH}_3)_3$), 3.25 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 3.41 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 4.51 (s, 2H, CH_2Ph), 7.36 (m, 5H, Ar-H); δ_{C} (75MHz) -1.6 ($\text{Si}(\text{CH}_3)_3$), 35.4 ($\text{CH}_2\text{Si}(\text{CH}_3)_3$), 42.5 (CH_2Ph), 45.5 ($\text{NCH}_2\text{CH}_2\text{N}$), 48.7 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.2, 128.1, 128.5 ($3 \times \text{Ar-CH}$), 137.5 (Ar-C), 161.8 (NC=O); m/z (EI) 262 (M^{++} , 12%), 248 (5%), 247 (18%), 189 (4%), 171 (8%), 155 (7%), 100 (9%), 91 (100%), 73 (77%), 65 (16%), 45 (22%), 43 (13%); (Found: (EI): M^{++} 262.1503; $\text{C}_{14}\text{H}_{22}\text{N}_2\text{OSi}$ requires M^{++} 262.1501). Also isolated was 1-benzyl-3-methyl-tetrahydroimidazol-2-one **154** as a colourless oil (0.44 g; 27%); δ_{H} (300MHz) 2.82 (s, 3H, NCH_3), 3.13 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 3.18 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 4.37 (s, 2H, CH_2Ph); δ_{C} (75MHz) 31.4 (NCH_3), 42.2 (CH_2Ph), 44.9 ($\text{NCH}_2\text{CH}_2\text{N}$), 48.7 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.4, 127.7, 128.5 ($3 \times \text{Ar-CH}$), 137.3 (Ar-C), 161.5 (NC=O); m/z (EI) 190 (M^{++} , 30%), 161 (6%), 113 (13%), 99 (34%), 92 (9%), 91 (100%), 89 (11%), 77 (23%), 65 (34%), 56 (18%), 51 (16%), 43 (13%), 42 (44%), 39 (15%); (Found: (EI) M^{++} 190.1107; $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ requires M^{++} 190.1106).

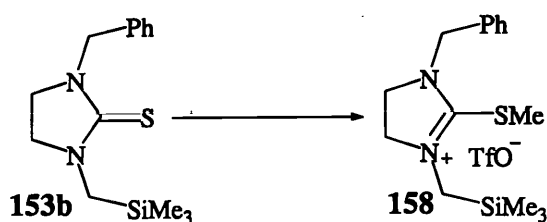
1-Benzyl-3-trimethylsilylmethyl-4,5-tetrahydroimidazol-2-thione



To a solution of the 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one (0.86 g; 3.28 mmol) in dry *ortho*-xylene (30 ml) was added portionwise Lawesson's Reagent (1.32 g; 3.28 mmol). The mixture was heated at reflux for 26 h after which time it was allowed to cool to RT. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (25 : 75 v/v) as eluant to afford the *title compound* as a yellow gum (0.63 g; 69%): ν_{\max} (film) / cm^{-1} 3030, 2938, 1696, 1498, 1445, 1404, 1252, 1056, 760, 702; δ_{H} (300MHz) 0.20 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 3.12 (s, 2H, $\text{CH}_2\text{SiC}(\text{CH}_3)_3$), 3.21 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$) 3.25 (m, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 4.92 (s, 2H, CH_2Ph), 7.32 (m, 5H, Ar-H); δ_{C} (75MHz) -1.4 ($\text{Si}(\text{CH}_3)_3$), 39.3 (CH_2Ph), 45.3 ($\text{NCH}_2\text{Si}(\text{CH}_3)_3$), 48.5 ($\text{NCH}_2\text{CH}_2\text{N}$), 52.1 ($\text{NCH}_2\text{CH}_2\text{N}$), 127.5, 128.1, 128.6 ($3 \times \text{Ar-CH}$), 136.8 (Ar-C), 182.9 ($\text{C}=\text{S}$); m/z (EI) 278 (M^{+} , 10%), 264 (5%), 263 (21%), 92 (8%), 91 (100%), 73 (69%), 65 (20%), 45 (23%); (Found: (EI): M^{+} 278.1287; $\text{C}_{14}\text{H}_{22}\text{N}_2\text{SSi}$ requires M^{+} 278.1273).

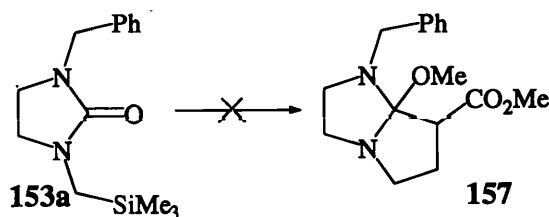
1-Benzyl-3-trimethylsilylmethyl-2-methylthio-4,5-tetrahydroimidazolium

trifluoromethane sulfonate



To a solution of 1-benzyl-3-trimethylsilylmethyl-4,5-tetrahydroimidazol-2-thione (0.10 g; 0.36 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere, was added neat methyl trifluoromethanesulfonate (0.02 ml; 0.43 mmol) and the solution allowed to stir at RT for 1 h. The solvent was removed under reduced pressure to yield the *title* compound as a yellow gum (0.15 g; 94%): δ_{H} (300MHz) 2.49 (s, 3H, SCH₃), 3.14 (s, 2H, CH₂Si(CH₃)₃), 3.72 (m, 2H, NCH₂CH₂N), 3.76 (m, 2H, NCH₂CH₂N), 4.64 (s, 2H, PhCH₂), 7.24 (m, 5H, Ar-H); δ_{C} (75MHz) -1.1 (Si(CH₃)₃), 17.3 (SCH₃), 44.2 (CH₂Ph), 49.1 (NCH₂ Si(CH₃)₃), 54.2 (NCH₂CH₂N), 55.6 (NCH₂CH₂N), 127.4, 128.3, 128.6 (3 × Ar-CH), 137.7 (Ar-C).

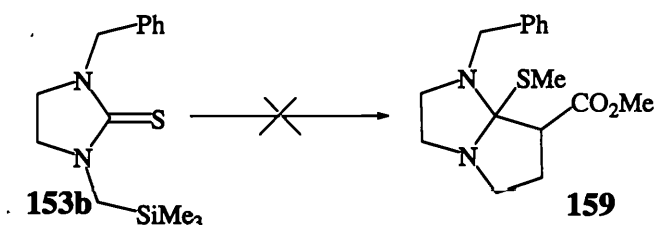
Attempted synthesis of methyl 1-benzyl-7a-methoxyhexahydro-1H-pyrrolo[1,2-*a*]imidazole-7-carboxylate



Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.14 ml; 1.23

mmol) to a solution of 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-one (0.27 g; 1.03 mmol) in dry dichloromethane (10 ml) under nitrogen. The solution was stirred at RT for 8 h. The solvent was removed and replaced by dry glyme (45 ml). Methyl acrylate (0.28 ml; 3.09 mmol) was added to the reaction mixture and the resulting solution stirred for 10 min at RT and then transferred into a flask containing flamed dried caesium fluoride (0.39 g; 2.57 mmol). The resulting mixture was the left stirring for 48 h. The solvent was removed under reduced pressure and residue subjected to silica gel column chromatography using ethyl acetate / hexane (3 : 7 v/v) as eluant but none of the *title compound* was isolated.

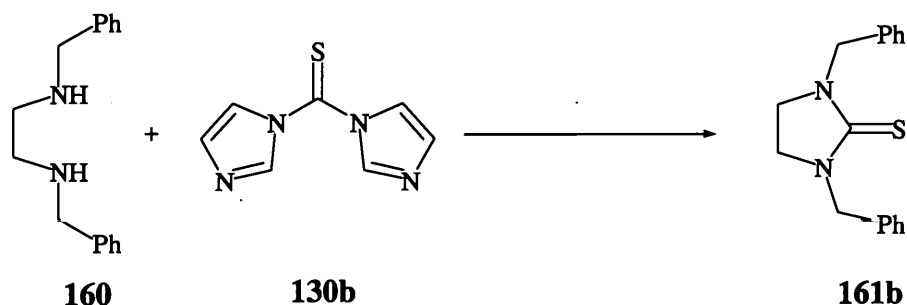
Attempted synthesis of methyl 1-benzyl-7a-methylthiohexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-carboxylate



Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.30 ml; 2.62 mmol) to a solution of 1-benzyl-3-trimethylsilylmethyltetrahydroimidazol-2-thione (0.61 g; 2.19 mmol) in dry dichloromethane (10 ml) under nitrogen. The solution was stirred at RT for 8 h and the solvent removed under reduced pressure and replaced by dry glyme (45 ml). Methyl acrylate (0.59 ml; 6.57 mmol) was added to the reaction mixture, the resulting solution stirred for 10 min at RT and then transferred into a flask containing flamed dried caesium fluoride (0.80 g; 5.45 mmol). The resulting mixture was the left stirring for 48 h.

The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (3 : 7 v/v) as eluant but none of the *title compound* was isolated.

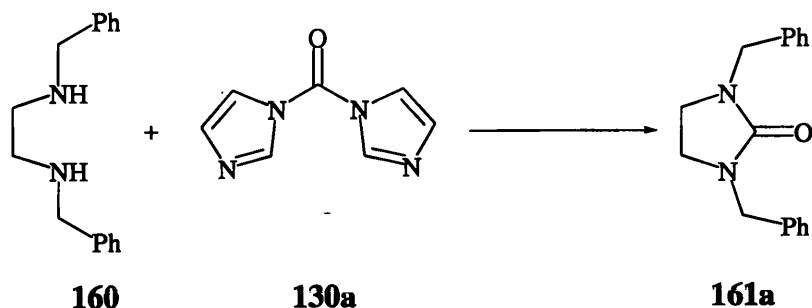
1,3-Dibenzyltetrahydroimidazol-2-thione



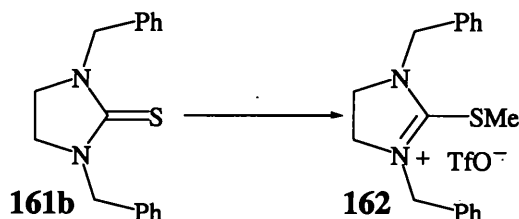
To a solution of commercial N,N'-dibenzyl-1,2-diaminoethane (0.40 g; 1.60 mmol) in dry THF (20 ml) under nitrogen was added a solution of 1,1'-thiocarbonyldiimidazole (0.38 g; 1.92 mmol) in dry THF (10 ml). The resulting solution was stirred at RT for 18 h before the solvent was evaporated under reduced pressure. The residue was washed with dilute hydrochloric acid (2 M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried (MgSO₄), filtered and the solvent evaporated under reduced pressure to afford the *title compound* as a yellow solid (0.44 g; 98%): m.p. 87-92°C (lit.,¹²¹ 90°C); ν_{\max} (nujol) / cm⁻¹ 2927, 2855, 1494, 1462, 1378, 1359, 1334, 1268, 1240, 731; δ_{H} (400MHz) 3.40 (s, 4H, NCH₂CH₂N) 4.92 (s, 4H, 2 × CH₂Ph), 7.38 (m, 10H, Ar-H); δ_{C} (100MHz) 45.69 (PhCH₂), 52.09 (NCH₂CH₂N), 127.98, 128.49, 128.97 (3 × Ar-CH) 136.74 (Ar-C), 184.82 (NC=S); m/z (EI) 282 (M^{•+}, 20%), 191 (30%), 105 (9%), 91

(100%), 65 (16%), 56 (5%); (Found: (EI): M^{*+} 282.1188; $C_{17}H_{18}N_2S$ requires M^{*+} 282.1191).

1,3-Dibenzyltetrahydroimidazol-2-one

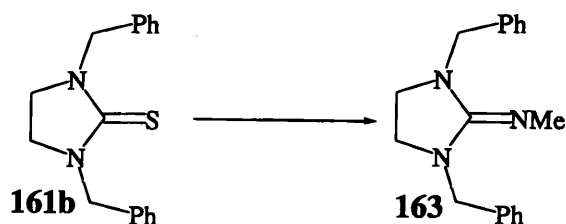


To a solution of N,N'-dibenzyl-1,2-diaminoethane (0.40 g; 1.6 mmol) in dry THF (20 ml) under nitrogen was added a solution of 1,1'-carbonyldiimidazole (0.38 g; 1.92 mmol) in dry THF (10 ml). The resulting solution was stirred at RT for 18 h before the solvent was evaporated under reduced pressure. The product washed with dilute hydrochloric acid (2 M; 50 ml) and extracted with dichloromethane (2 × 50 ml). The combined organic phases were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to afford the *title compound* as a white solid (0.41 g; 97%); m.p. 90-91°C (lit.,¹²² 93-94°C); ν_{max} (nujol) / cm^{-1} 2927, 2855, 1689, 1494, 1455, 1365, 1257, 711; δ_H (300MHz) 3.16 (s, 4H, NCH_2CH_2N), 4.41 (s, 4H, 2 × CH_2Ph), 7.32 (m, 10H, Ar-H); δ_C (75MHz) 42.2 ($PhCH_2$), 48.6 (NCH_2CH_2N), 127.5, 128.3, 128.6 (3 × Ar-CH), 137.4 (Ar-C), 161.1 (NC=O); m/z (EI) 266 (M^{*+} , 73%), 189 (4%), 175 (71%), 132 (9%), 118 (6%), 105 (8%), 91 (100%), 65 (15%); (Found: (EI): M^{*+} 266.1414; $C_{17}H_{18}N_2O$ requires M^{*+}

1,3-Dibenzyl-2-methylthio-4,5-dihydroimidazolinium trifluoromethanesulfonate

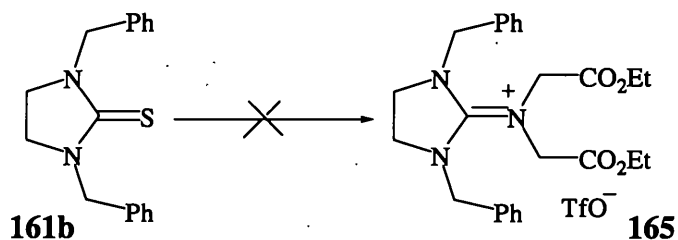
Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.09 ml; 0.85 mmol) to a solution of 1,3-dibenzyltetrahydroimidazol-2-thione (0.20 g; 0.71 mmol) in dry dichloromethane (10 ml). The solution was stirred at RT for 1 h. The solvent was then removed under reduced pressure to afford the *title compound* as a yellow oil (0.32 g; 100%): ν_{max} (film) / cm^{-1} 3034, 2944, 1591, 1574, 1499, 1455, 1357, 1262 (br), 1225 (br), 1157 (br), 1031, 756, 738, 703; δ_{H} (300MHz) 2.86 (s, 3H, SCH₃), 3.90 (s, 4H, 2 × NCH₂CH₂N), 4.92 (s, 4H, 2 × CH₂Ph), 7.29 (m, 5H, Ar-H), 7.37 (m, 5H, Ar-H); δ_{C} (75MHz) 16.47 (SCH₃), 47.8 (2 × CH₂Ph), 53.3 (2 × NCH₂), 127.6, 127.9, 128.5 (6 × Ar-CH), 132.4 (2 × Ar-C), 167.2 (NCS); (Found: (ES, M-CF₃SO₃⁻): M⁺ 297.1422; C₁₉H₂₁F₃N₂O₃S₂ requires M⁺ 297.1425).

1,3-Dibenzyl-2-methyliminotetrahydroimidazole



Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.13 ml; 1.10 mmol) to a solution of 1,3-dibenzyltetrahydroimidazol-2-thione (0.26 g; 0.92 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere and the solution stirred at RT for 1 h. Methyl amine (2M solution in THF; 0.69 ml; 1.38 mmol) was added and the resulting solution heated at reflux for 18 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using isopropylamine / chloroform (2 : 98 v/v) as solvent system to afford the *title compound* as a yellow gum (0.10 g; 40%): ν_{\max} (film) / cm^{-1} 2870, 1490, 1226, 1220; δ_{H} (300MHz) 3.01 (s, 3H, NCH_3), 3.44 (s, 4H, NCH_2CH_2), 4.53 (s, 4H, $2 \times \text{CH}_2\text{Ph}$), 7.26 (m, 6H, Ar-H), 7.30 (m, 4H, Ar-H); δ_{C} (75MHz) 30.9 ($2 \times \text{N}=\text{CH}_3$), 46.7 ($2 \times \text{CH}_2\text{Ph}$), 50.7 ($2 \times \text{NCH}_2\text{CH}_2\text{N}$), 127.5, 128.4, 129.1 ($3 \times \text{Ar-CH}$), 133.8 (Ar-C), 158.5 ($\text{NC}=\text{NCH}_3$); m/z (EI) 279 (M^{+} , 24%), 250 (10%), 207 (16%), 125 (19%), 111 (35%), 97 (58%), 91 (23%), 83 (57%), 69 (77%), 57 (100%), 49 (27%), 43 (76%), 39 (15%), 29 (26%); (Found: (EI): MH^{+} 280.1738; $\text{C}_{17}\text{H}_{21}\text{N}_3$ requires MH^{+} 280.1735).

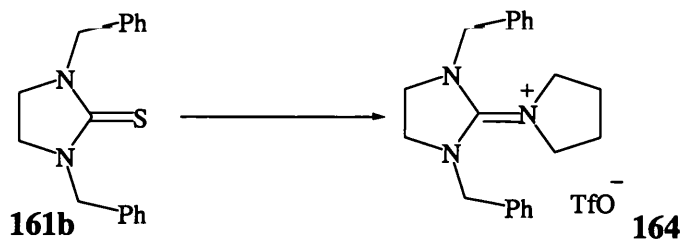
Attempted synthesis of 1,3-dibenzyl-2-[bis(ethoxycarbonylmethyl)imino]tetrahydroimidazolinium trifluoromethanesulfonate



Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.09 ml; 0.84 mmol) to a solution of 1,3-dibenzyltetrahydroimidazol-2-thione (0.20 g; 0.70 mmol) in dry dichloromethane (10 ml) under a nitrogen atmosphere and the solution stirred at RT for 1 hour. The solvent was removed under reduced pressure, dry toluene (20 ml) was injected into the reaction flask and the solution treated with diethyl imino-diacetate (0.15 ml; 0.84 mmol). The resulting mixture was heated at reflux for 72 h. The solvent was removed under reduced pressure and the residue subjected to NMR analysis. Only starting material **161b** peaks could be observed.

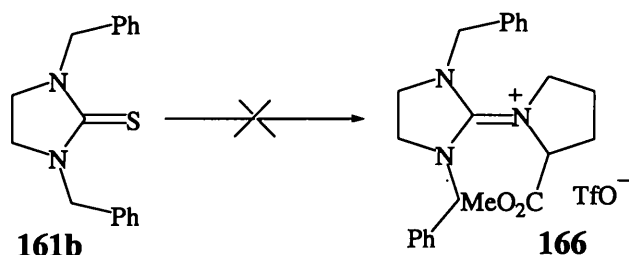
**1,3-Dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolinium
sulfonate**

trifluoromethane



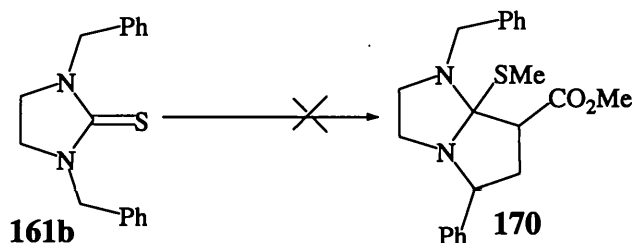
Via a syringe was added dropwise methyl trifluoromethanesulfonate (0.12 ml; 1.0 mmol) to a solution of 1,3-dibenzyltetrahydroimidazol-2-thione (0.25 g; 0.88 mmol) in dry dichloromethane (15 ml) under nitrogen, and the solution stirred at RT for 1 hour. The solvent was removed under reduced pressure, dry THF (25 ml) was added under nitrogen to the residue and the resulting solution treated with pyrrolidine (0.09 ml; 1.0 mmol). The resulting solution was heated to reflux for 26 h and then allowed to cool to RT. The solvent was removed under reduced pressure to afford the *title compound* as a brown oil (0.32 g; 77%): δ_{H} (300MHz) 1.86 (t, 4H, $J = 6.6$, CH_2CH_2 pyrrolidine), 3.61 (t, 4H, $J = 6.6$, NCH_2 pyrrolidine), 3.84 (s, 4H, $\text{PhNCH}_2\text{CH}_2\text{NPh}$), 4.76 (s, 4H, $2 \times \text{CH}_2\text{Ph}$), 7.26 (m, 6H, Ar- H), 7.39 (m, 4H, Ar- H); δ_{C} (75MHz) 25.5 (CH_2CH_2), 49.4 (NCH_2), 50.8 ($2 \times \text{CH}_2\text{Ph}$), 53.4 (CH_2N), 126.3, 128.2, 129.3 ($3 \times \text{Ar-CH}$), 134.8 (Ar-C), 162.4 (NC=N).

Attempted synthesis of 1-(1,3-dibenzyltetrahydroimidazole-2-ylidene)-2-methoxycarbonyl-pyrrolidinium trifluoromethanesulfonate



Prepared as for 1,3-dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolium trifluoromethane sulfonate **164** but using 1,3-dibenzyltetrahydroimidazol-2-thione (0.20 g; 0.71 mmol), methyl trifluoromethanesulfonate (0.09 ml; 0.85 mmol) and proline methyl ester (0.08 g; 0.85 mmol) in place of pyrrolidine. The crude residue was analysed by NMR where the expected peaks for the formation of the *title compound* were not observable.

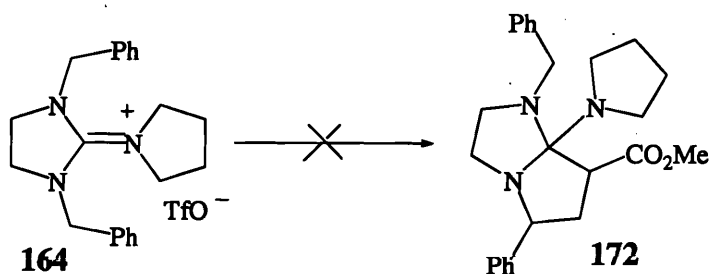
Attempted synthesis of methyl 1-benzyl-7a-methylthio-5-phenylhexahydro-1H-pyrrolo[1,2-*a*]imidazole-7-carboxylate



Methyl trifluoromethanesulfonate (0.10 ml; 0.93 mmol) was added to a solution of

1,3-dibenzyltetrahydroimidazol-2-thione (0.22 g; 0.78 mmol) in dry THF under nitrogen at RT and the solution stirred for 1 h. The solution was then cooled to -78°C before the dropwise addition of *sec*-BuLi (1.3M solution in hexanes; 0.72 ml; 0.93 mmol) followed by the addition of methyl acrylate (0.21 ml; 2.34 mmol). The resulting solution was then warmed to RT and then heated at reflux for 12 h. Removal of the solvent under reduced pressure and subjection of the crude residue to silica gel column chromatography afforded none of the *title compound*.

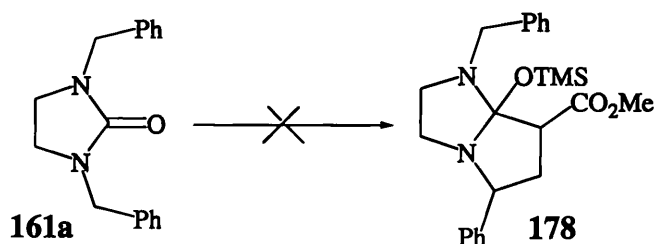
Attempted synthesis of 1-benzyl-5-phenyl-7-methoxycarbonyl-7a-(pyrrolidin-1-yl)hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole



To a solution of 1,3-dibenzyl-2-(tetramethyleneimino)tetrahydroimidazolium trifluoromethane sulfonate **164** (0.40 g; 0.85 mmol) in dry THF (20 ml) at -78°C was added *sec*-BuLi (1.3M solution in hexanes; 0.78 ml; 1.0 mmol). The solution was kept at -78°C for 20 min and treated with excess methyl acrylate (0.23 ml; 2.55 mmol). The resulting solution was allowed to warm up to RT and heated at reflux for 8 h. The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (3 : 7 v/v) as eluant but none of the *title*

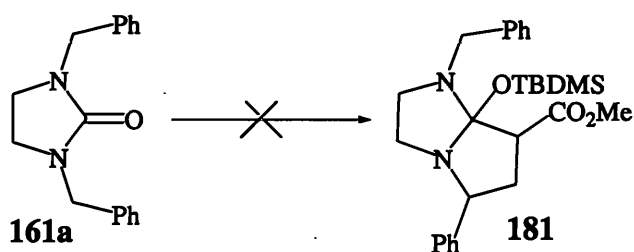
compound was isolated.

Attempted synthesis of methyl 1-benzyl-5-phenyl-7a-(trimethylsiloxy)hexahydro-1H-pyrrolo[1,2-*a*]imidazole-7-carboxylate



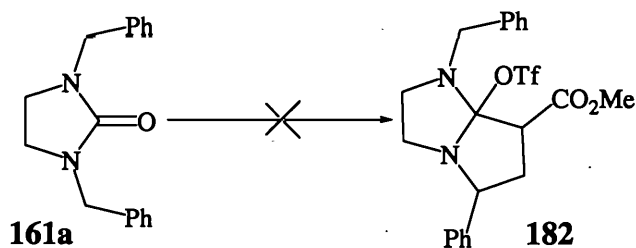
To a solution of 1,3-dibenzyltetrahydroimidazol-2-one (0.42 g; 1.58 mmol) in dry THF (15 ml) at RT and under nitrogen, was added trimethylsilyltrifluoromethane sulfonate (0.36 ml; 1.89 mmol). The solution was stirred for 30 min at RT and then cooled to -78°C . *sec*-BuLi (1.3M solution in hexanes; 1.45 ml; 1.89 mmol) was added dropwise followed by the addition of methyl acrylate (0.43 ml; 4.74 mmol). The reaction mixture was allowed to warm up to RT and heated at reflux for a further 8 h. Subjection of the residue to column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant afforded none of the *title compound*.

Attempted synthesis of methyl 1-benzyl-5-phenyl-7a-(*tert*-butyldimethylsiloxy) hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-carboxylate



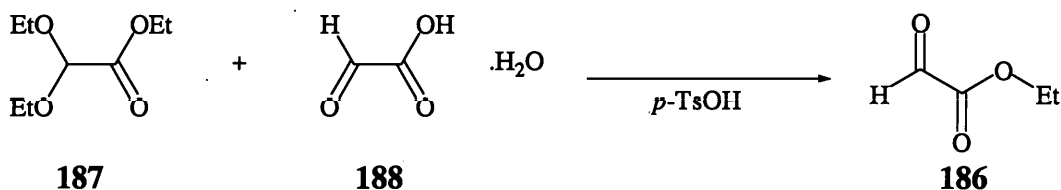
To a solution of 1,3-dibenzyltetrahydroimidazol-2-one (0.47 g; 1.76 mmol) in dry THF (15 ml) at RT and under nitrogen, was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.48 ml; 2.11 mmol). The solution was stirred for 30 min and then cooled to -78°C. *sec*-BuLi (1.3M solution in hexanes; 1.63 ml; 2.11 mmol) was added dropwise followed by the addition of methyl acrylate (0.48 ml; 5.28 mmol). The reaction mixture was allowed to warm up to RT and then heated at reflux for a further 8 h. Subjection of the residue to silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant afforded none of the *title* compound.

Attempted synthesis of methyl 1-benzyl-5-phenyl-7a-(trifluoromethanesulfonyloxy) hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-carboxylate



To a solution of 1,3-dibenzyltetrahydroimidazol-2-one (0.25 g; 0.94 mmol) in dry THF (20 ml) under nitrogen, was added (in a glove box) trifluoromethane sulfonic anhydride (0.19 ml; 1.13 mmol) and the resulting solution allowed to stir at RT for 2 h before methyl acrylate (0.25 ml; 2.82 mmol) was added. The mixture was heated at reflux and *sec*-BuLi (1.3 M solution in hexanes; 0.86 ml; 1.13 mmol) was added over a period of 4 h. Reflux was continued for a further 4 h and the mixture was allowed to cool to RT. Subjection of the residue to by silica gel column chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant afforded none of the *title compound*.

Ethyl glyoxalate⁹⁵

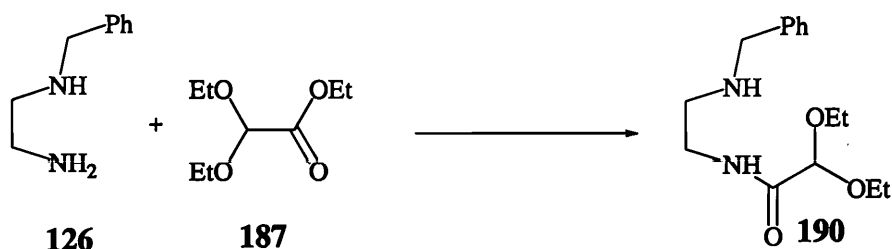


Ethyl diethoxyacetate (12.90 g; 73 mmol), glyoxylic acid monohydrate (6.50 g;

70.0 mmol) and *p*-toluenesulphonic acid (200.0 mg; 1.0 mmol) were combined and the resulting mixture refluxed for 27 h using an air condenser. The resultant clear homogeneous syrup was cooled (ice-methanol), stirred vigorously while phosphorous pentoxide (8.00 g; 28.0 mmol) was added portionwise and the subsequent mixture heated at 90-100°C for a further 2 h. Distillation under reduced pressure afforded the title compound as a viscous and colourless liquid (7.14 g; 89%): b.p. 72-78°C / 25mmHg

(Lit.,⁹⁵ 49°C / 35 mmHg); ν_{\max} (film) / cm^{-1} 3450, 3168, 1590, 1586, 1290; δ_{H} (400MHz) 1.46 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$) 4.47 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 9.47 (s, 1H, CHO); 1.46 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$) 4.47 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 9.47 (s, 1H, CHO); δ_{C} (100MHz) 13.90 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 63.11 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 159.44 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 183.91 (CHO); m/z 103 (EI) (M^{*+} , 54%), 85 (25%), 83 (33%), 75 (100%), 57 (34%).

N-(2-Benzylaminoethyl)-2,2-diethoxyethanamide



Ethyl diethoxyacetate (1.06 g; 6.0 mmol) was added to a stirred solution of 1-benzyl-diaminoethane (1.00 g; 6.0 mmol) in diethyl ether (70 ml) and the resulting solution stirred at RT for 24 h. The solution was then washed with water (20 ml) and extracted with diethyl ether (2×30 ml). The combined organic extracts were dried (MgSO_4) and the solvent evaporated under reduced pressure. The residue was then purified by silica gel column chromatography using chloroform / methanol (10 : 90 v/v) as eluant to afford the

title compound as a colourless oil (0.80 g; 47%): δ_{H} (400MHz) 1.26 (t, 6H, $J = 6.9$, $2 \times \text{OCH}_2\text{CH}_3$), 2.79 (t, 2H, $J = 6.0$, $\text{NHCH}_2\text{CH}_2\text{N}$), 3.39 (t, 2H, $J = 6.0$, $\text{NHCH}_2\text{CH}_2\text{N}$), 3.58 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 3.73 (s, 2H, CH_2Ph), 4.75 (s, 1H, $\text{COCH}(\text{OEt})_2$), 7.22 (m, 5H, Ar- H); δ_{C} (100MHz) 15.1 ($2 \times \text{OCH}_2\text{CH}_3$), 38.6 (CH_2Ph), 47.7 ($\text{NHCH}_2\text{CH}_2\text{N}$), 53.33 ($\text{NHCH}_2\text{CH}_2\text{N}$), 62.5 ($2 \times \text{OCH}_2\text{CH}_3$), 98.6 ($\text{COCH}(\text{OEt})_2$), 127.0, 128.00, 128.3 ($3 \times \text{Ar-CH}$), 136.1 (Ar-C), 162.9 (NC=O); m/z (EI) 281 (MH^+ , 20%), 205 (35%), 189 (65%), 133 (38%), 120 (57%), 106 (22%), 103 (49%), 91 (100%), 75 (28%), 65 (10%).

1-Benzyl-2-formyl-4,5-dihydroimidazole

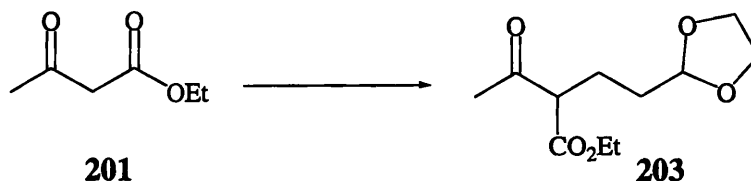


A solution of N-(2-benzylaminoethyl)-2,2-diethoxyethanamide **190** (0.30 g; 1.1 mmol) in ethanol (20 ml) was stirred at RT for 14 h and then quenched with a solution of sodium thiosulfate (2.79 g) in H_2O (50 ml). Stirring was continued for 1 h then the solution extracted with dichloromethane (2×50 ml). The organic phase was dried (MgSO_4) and evaporated under reduced pressure to afford the *title compound* as a yellow gum (0.12g; 60%): ν_{max} (film) / cm^{-1} 3171 (br), 3030, 1641, 1524, 1456, 1379, 1297, 1203, 919, 731; δ_{H} (400MHz) 3.74 (t, 3H, $J = 6.4$, $\text{NCH}_2\text{CH}_2\text{N}$), 3.97 (t, 3H, $J = 6.4$, $\text{NCH}_2\text{CH}_2\text{N}$), 4.80 (s, 2H, CH_2Ph), 7.29 (m, 5H, Ar- H), 8.94 (s, 1H, CHO); δ_{C} (100MHz) 40.3 (CH_2Ph), 51.7

(NCH₂CH₂N), 52.7 (NCH₂CH₂N), 127.3, 128.1, 128.4 (3 × Ar-CH), 136.1 (Ar-C), 161.2 (N=CCHO), 200.1 (CHO); *m/z* (EI) 189 (MH⁺, 13%), 161 (60%), 91 (100%), 81 (25%), 69 (30%), 57 (27%), 41 (19%), 28 (20%); (Found: (EI): MH⁺ 189.1028; C₁₁H₁₂N₂O requires MH⁺ 189.1028)

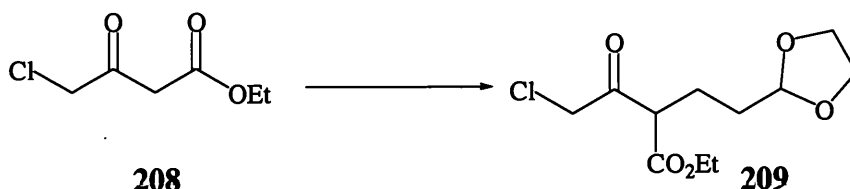
3.2 Intramolecular approach experimental

2-(3-Ethoxycarbonyl-4-oxopentyl)dioxalane¹⁰⁵



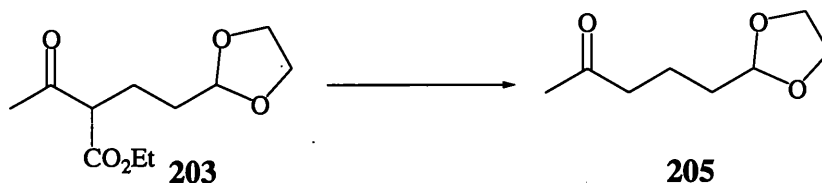
The title compound was prepared using a slight variation of a literature procedure.¹⁰⁵ To an ice-cold suspension of NaH (3.31 g; 144 mmol) in dry THF (300 ml) and was added dropwise ethyl acetoacetate **201** (14.68 ml; 120.0 mmol). The resulting mixture was refluxed and of commercial 2-(2-bromoethyl)-1,3-dioxolane **203** (16.25 ml; 144.0 mmol) was added dropwise over a period of 30 min. Heating was continued for a further 36 h. The reaction mixture was then allowed to cool down to RT and filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate / hexane (25 : 75 v/v) as eluant to afford the title compound as an orange oil (11.92 g; 45%): ν_{max} (film) / cm^{-1} 2981, 2888, 1741, 1717, 1144, 1030; δ_{H} (300MHz) 1.22 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.59 (m, 2H, OCHCH_2), 1.94 (q, 2H, $J = 7.7$, $\text{OCHCH}_2\text{CH}_2$), 2.18 (s, 3H, CH_3CO), 3.43 (t, 1H, $J = 7.5$, COCHCO_2Et), 3.75 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.82 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.11 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.79 (t, 1H, $J = 4.4$, $\text{OCH}_2\text{CH}_2\text{OCHCH}_2$); δ_{C} (75MHz) 14.1 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 22.3 ($\text{OCHCH}_2\text{CH}_2$), 28.9 (CH_3CO), 31.2 (OCHCH_2), 59.2 (COCHCO_2Et), 61.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 64.9 ($2 \times \text{OCH}_2$), 103.8 (OCHO), 169.6 (CO_2Et), 201.9 (CH_3COCH).

Attempted synthesis of 2-(5-chloro-3-ethoxycarbonyl-4-oxopentyl)dioxalane



To an ice-cold suspension of NaH (0.34 g; 14.4 mmol) in dry THF (40 ml) was added dropwise ethyl 4-chloroacetoacetate **208** (1.64 ml; 12.0 mmol). The resulting mixture was refluxed then 2-(2-bromoethyl)-1,3-dioxolane **202** (1.57 ml; 13.3 mmol) was added dropwise over a period of 30 min. The solution was unchanged by TLC analysis after 16 h reflux and after work-up afforded the starting material **208**.

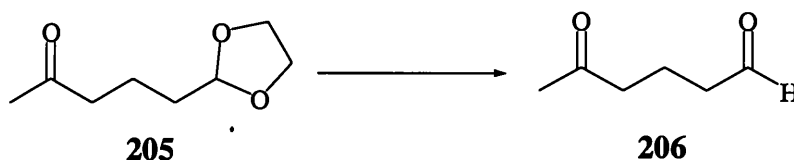
2-(4-Oxopentyl)dioxalane¹⁰⁵



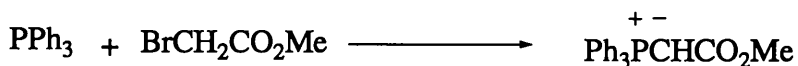
A mixture of 2-(3-ethoxycarbonyl-4-oxopentyl)dioxolane **203** (0.56 g; 2.43 mmol) and 5% aqueous sodium hydroxide solution (5.82 ml; 7.29 mmol) was stirred under reflux for 16 h. After cooling, the reaction mixture was extracted with diethyl ether (3 × 25 ml), the combined organic extracts dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the crude keto-acetal. Purification by column chromatography using ethyl acetate / hexane (25 : 75 v/v) as eluant afforded the title compound as a brown oil (0.34 g; 89%): ν_{max} (film) / cm⁻¹ 2956, 2886, 1714, 1412, 1363, 1227, 1141, 1030, 970, 902; δ_{H} (300MHz) 1.71 (m, 4H, CH₂CH and CH₂CH₂CH), 2.16 (s, 3H, CH₃CO), 2.49 (t, 2H, *J* = 6.9, CH₃COCH₂), 3.88 (m, 2H, OCH₂CH₂O), 3.95 (m, 2H, OCH₂CH₂O), 4.83 (t,

^1H , $J = 4.2\text{Hz}$, OCHO); δ_{C} (75MHz) 18.2 (COCH_2CH_2), 29.9 ($\text{CH}_2\text{CH}_2\text{CH}$), 33.0 (CH_3CO), 43.3 (CH_3COCH_2), 64.8 ($\text{OCH}_2\text{CH}_2\text{O}$), 104.2 (OCHO), 208.6 (CH_3COCH_2); m/z (EI) 159 (MH^+ , 54%), 115 (82%), 84 (21%), 73 (100%), 51 (12%), 49 (41%), 43 (22%); (Found: (EI) MH^+ 159.1021; $\text{C}_8\text{H}_{14}\text{O}_3$ requires MH^+ 159.1021)

5-Oxo-hexanal¹⁰⁵



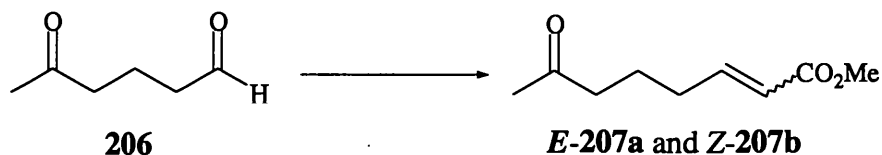
To a cooled solution of the keto-acetal **205** (6.4 g; 40.0 mmol) in THF (100 ml) was added, dropwise with stirring, 1 M hydrochloric acid (120.0 ml; 120.0 mmol). The solution was heated at 50°C for 5 h and then allowed to cool to RT. After neutralisation with NaHCO_3 (10.08 g; 120.0 mmol) the product was extracted with dichloromethane. The organic phase was dried (MgSO_4) and evaporated under reduced pressure to afford the crude title compound as a colourless liquid, but which was used directly without further purification: δ_{H} (300MHz) 1.80 (m, 2H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CO}$), 2.16 (s, 3H, CH_3CO), 2.55 (m, 4H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CO}$), 9.70 (s, 1H, CH_2CHO).

Methyl (triphenylphosphoranylidene)acetate¹⁰⁶

210

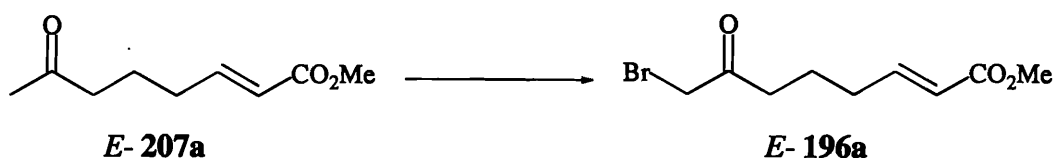
Using a slight variation of literature methodology,¹⁰⁶ a solution of triphenylphosphine (25 g; 0.095 mol) in dry toluene (150 ml) was added dropwise methyl bromoacetate (9.90 ml; 0.10 mol). The resulting solution was refluxed for 2 h and then cooled to RT. The white solid was filtered, washed with hexane and then dissolved in cold water (1.5 l) and dichloromethane (1.0 l) was added to the solution. The resulting two phase mixture was stirred vigorously whilst excess NaOH (1 M; 50 ml) was added dropwise. When the solution was alkaline, the organic phase was separated and the aqueous solution extracted with dichloromethane (3 × 400 ml). The combined organic extracts were dried (MgSO₄), filtered and the solvent removed under reduced pressure until the initial formation of a precipitate could be observed. Hexane (30 ml) was then added, the flask sonic and the resulting solid was filtered and washed with hexane to afford the title compound as a white solid (28 g; 88%): m.p. 160-161°C (lit.,¹²³ 162-163°C); δ_{H} (300MHz) 2.94 (d, 1H, $J = 21.7$ Ph₃PCH), 3.58 (s, 3H, CO₂CH₃), 7.40-7.65 (m, 15H, Ar-H).

Methyl *E*-7-oxooct-2-enoate and methyl *Z*-7-oxooct-2-enoate¹⁰⁵



A solution of methyl (triphenylphosphoranylidene)acetate **210** (17.72 g; 23.1 mmol) in dichloromethane (50 ml) was added dropwise with stirring to a solution of the crude 5-oxo-hexanal **206** (2.44 g; 21.0 mmol). The reaction mixture was stirred overnight at RT. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate / hexane (2 : 8 v/v) as eluant to afford the title compound separable mixture of *E*- and *Z*- isomers (8:1 *E* : *Z*) and as a colourless oil (3.25 g; 90%): ν_{\max} (film) / cm^{-1} 2980, 1716, 1650, 1443, 1367, 1273, 1190, 1047, 984, 708; (*E*-isomer) δ_{H} (300MHz) 1.74 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.11 (s, 3H, CH_3CO), 2.23 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 2.43 (t, 2H, $J = 7.3$, CH_3COCH_2), 3.70 (s, 3H, CO_2CH_3), 5.79 (dt, 1H, $J = 1.6$, 15.8, $\text{CH}=\text{CHCO}_2\text{Me}$), 6.90 (dt, 1H, $J = 6.9$, 15.8, $\text{CH}=\text{CHCO}_2\text{Me}$); δ_{C} (75MHz) 21.6 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 30.8 ($\text{CH}_2\text{CH}=\text{CH}$), 32.3 (CH_3CO), 41.1 (CH_3COCH_2), 51.7 (CO_2CH_3), 122.2 ($\text{CH}=\text{CHCO}_2\text{Me}$), 147.6 ($\text{CH}=\text{CHCO}_2\text{Me}$), 166.4 (CO_2CH_3), 208.3 (CH_3COCH_2); (*Z*-isomer) δ_{H} (300MHz) 1.79 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.21 (s, 3H, CH_3CO), 2.67 (dq, 2H, $J = 1.6$, 7.5, $\text{CH}_2\text{CH}=\text{CH}$), 2.70 (t, 2H, $J = 7.3$, CH_3COCH_2), 3.70 (s, 3H, CO_2CH_3), 5.82 (dt, 1H, $J = 1.6$, 11.5, $\text{CH}=\text{CHCO}_2\text{Me}$), 6.19 (dt, 1H, $J = 7.7$, 11.5, $\text{CH}=\text{CHCO}_2\text{Me}$); δ_{C} (75MHz) 21.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 27.6 ($\text{CH}_2\text{CH}=\text{CH}$), 38.7 (CH_3COCH_2), 51.6 (CO_2CH_3), 120.2 ($\text{CH}=\text{CHCO}_2\text{Me}$), 147.9 ($\text{CH}=\text{CHCO}_2\text{Me}$), 167.3 (CO_2CH_3), 202.1 (CH_3COCH_2); m/z (EI) 171 (MH^+ , 12%), 160 (15%), 158 (100%), 138 (8%), 113 (10%), 95 (13%), 86 (25%), 84 (41%), 81 (15%), 68 (12%), 51 (31%), 49 (98%), 43 (100%); (Found: (EI): MH^+ 171.1021; $\text{C}_9\text{H}_{14}\text{O}_3$ requires MH^+ 171.1021).

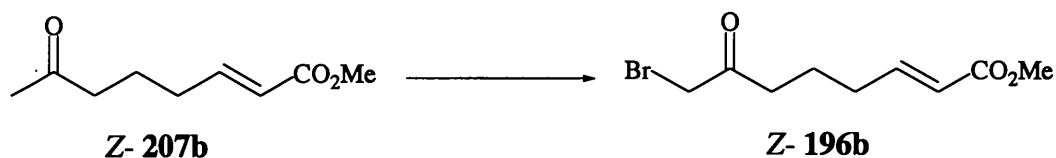
Methyl *E*-8-bromo-7-oxooct-2-enoate



All glassware used for this reaction was flame dried and all reagents were freshly distilled. A solution of methyl *E*-7-oxooct-2-enoate (1.63 g; 9.58 mmol) in dry THF (10 ml) at -78°C was added dropwise to a freshly prepared solution of LDA (1.2 eq; 11.5 mmol), prepared from *n*-BuLi (2.5M solution in hexanes; 4.60 ml; 11.5 mmol) and diisopropylamine (1.74 ml; 12.4 mmol), in dry THF (10 ml) at -78°C . The resulting mixture was allowed to stir at -78°C for 20 min before a solution of chlorotrimethylsilane (6.07 ml; 47.9 mmol) in dry THF (5 ml) also at -78°C was added. After stirring for 5 min, triethylamine (6.67 ml; 4.84 g) was added and the mixture allowed to warm to RT. Saturated sodium hydrogen carbonate (3 ml) was added and the mixture extracted with diethyl ether (3×30 ml). The organic phase was dried (MgSO_4) and the solvent removed under reduced pressure to afford the crude silyl enol ether moiety, which was used directly without further purification, as a colourless liquid (1.85 g; 79%). A solution of the silyl enol ether (1.85 g; 7.60 mmol) in dry THF (10 ml) at -78°C was treated with solid NaHCO_3 (1.12 g; 13.41 mmol), and the mixture allowed to stir at that temperature for 10 min. *N*-Bromosuccinimide (2.21 g; 12.45 mmol) was then added portionwise and the resulting mixture stirred for 4 h at -78°C . The mixture was then warmed to RT and subsequently heated at 80°C for 2 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography using ethyl acetate / hexane (15 : 85 v/v) as eluant to afford the *title compound* as a dark liquid (0.85 g; 45%): ν_{max} (film) / cm^{-1} 2951, 1719, 1646, 1439, 1408, 1369, 1174, 1092, 1039; δ_{H} (300MHz) 1.80 (quin, 2H, $J =$

7.1, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.23 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 2.67 (t, 2H, $J = 7.1$, COCH_2), 3.79 (s, 3H, CO_2CH_3), 3.91 (s, 2H, BrCH_2CO), 5.82 (dt, 1H, $J = 1.6$, 15.6, $\text{CH}=\text{CHCO}_2\text{Me}$), 6.87 (dt, 1H, $J = 6.9$, 15.6, $\text{CH}=\text{CHCO}_2\text{Me}$); δ_{C} (75MHz) 21.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 31.1 ($\text{CH}_2\text{CH}=\text{CH}$), 34.1 (BrCH_2CO), 38.7 (COCH_2), 51.5 (CO_2CH_3), 121.8 ($\text{CH}=\text{CHCO}_2\text{Me}$), 147.9 ($\text{CH}=\text{CHCO}_2\text{Me}$), 166.8 (CO_2CH_3), 201.4 ($\text{BrCH}_2\text{COCH}_2$); m/z (CI) 266 (MNH_4^+ , 100%), 258 (14%), 244 (23%), 214 (8%), 202 (9%), 188 (93%), 171 (5%); (Found: (Cl^+) MNH_4^+ 266.0392; $\text{C}_9\text{H}_{13}\text{BrO}_3$ requires MNH_4^+ 266.0392).

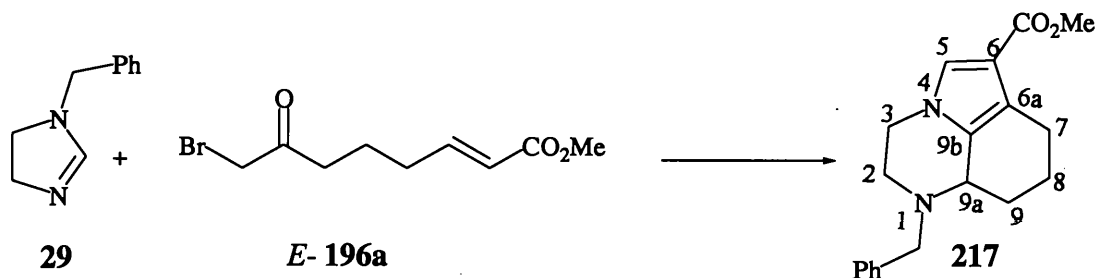
Methyl Z-8-bromo-7-oxooct-2-enoate



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a**, but using methyl *Z*-7-oxooct-2-enoate **207b** (0.90 g; 5.30 mmol), LDA (1.2 eq; 6.30 mmol), chlorotrimethylsilane (3.36 ml; 26.5 mmol), triethylamine (3.69 ml; 26.5 mmol), NaHCO_3 (0.62 g; 7.42 mmol) and *N*-bromosuccinimide (1.22 g; 6.89 mmol). Purification of the crude residue by column chromatography using ethyl acetate / hexane (15 : 85 v/v) as eluant afforded the *title compound* as a dark liquid (0.60 g; 45%): ν_{max} (film) / cm^{-1} 2954, 1717, 1643, 1434, 1410, 1370, 1171, 1092, 1039; δ_{H} (300MHz) 1.76 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.23 (s, 3H, CH_3CO), 2.66 (dq, 2H, $J = 1.6$, 7.5, $\text{CH}_2\text{CH}=\text{CH}$), 2.72 (t, 2H, $J = 7.3$, COCH_2), 3.70 (s, 3H, CO_2CH_3), 3.75 (s, 2H, BrCH_2CO), 5.84 (dt, 1H, $J = 1.6$, 11.5, $\text{CH}=\text{CHCO}_2\text{Me}$), 6.23 (dt, 1H, $J = 7.7$, 11.5, $\text{CH}=\text{CHCO}_2\text{Me}$); δ_{C} (75MHz) 22.8 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 27.9 ($\text{CH}_2\text{CH}=\text{CH}$), 34.3 ($\text{BrCH}_2\text{COCH}_2$), 38.9 (CH_3COCH_2), 51.1

(CO₂CH₃), 120.4 (CH=CHCO₂Me), 148.9 (CH=CHCO₂Me), 167.2 (CO₂CH₃), 202.3 (CH₃COCH₂).

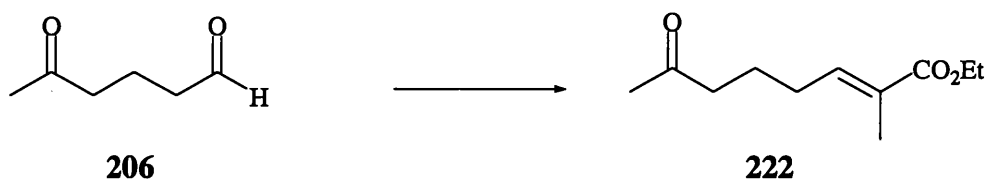
Methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate



To a solution of 1-benzyl-4,5-dihydroimidazole (0.15 g; 0.98 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of methyl *E*-8-bromo-7-oxooct-2-enoate (0.27 g; 1.08 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.17 ml; 1.17 mmol) was added dropwise over 4 h. The reaction was kept at reflux for a further 4 h. After cooling the reaction to RT and evaporating the solvent under reduced pressure, the residue was purified by silica gel column chromatography using ethyl acetate / hexane (3 : 7 v/v) as eluant to afford the *title compound* as a white solid (0.095 g; 31 %): m.p. 120-123°C; ν_{\max} (nujol) / cm⁻¹ 2881, 2944, 1735, 1697, 1524, 1463, 1390, 1248, 1172, 1098, 1051, 916, 732; δ_{H} (300MHz) 1.45 (dtd, 1H, *J* = 2.5, 11.6, 13.5, 9-CHH), 1.76 (dddt, 1H, *J* = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.12 (m, 1H, 8-CHH), 2.29 (m, 1H, 9-CHH), 2.49 (ddd, 1H, *J* = 7.5, 10.0, 12.5, 2-CHH), 2.66 (dddd, 1H, *J* = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.85 (dd, 1H, *J* = 6.4, 16.8, 7-CHH), 3.02 (ddd, 1H, *J* = 2.3, 3.9, 12.5, 2-CHH), 3.13 (d, 1H, *J* = 13.2, PhCH₂), 3.28 (br. d, 1H, *J* = 10.6, 9a-CH), 3.76 (s, 3H, CO₂CH₃), 3.85 (m, 2H, 3-CH₂), 4.25 (d, 1H, *J* = 13.2, PhCH₂), 7.12 (s, 1H, 5-CH), 7.23-

7.37 (m, 5H, Ar-*H*); δ_{C} (75MHz) 22.4, 22.5 (C-8 and C-7), 27.9 (C-9), 44.9 (C-2), 49.7 (C-3), 50.6 (CO₂CH₃), 57.3 (PhCH₂), 59.7 (C-9a), 113.8 (C-6a), 117.0 (C-6), 124.3 (C-5), 127.2, 128.4, 129.0 (3 \times Ar-CH), 130.2 (C-9b), 138.4 (Ar-C), 165.9 (CO₂CH₃); *m/z* (EI) 311 (MH⁺, 10%), 283 (10%), 282 (41%), 191 (39%), 161 (6%), 91 (100%), 49 (21%), 43 (17%); (Found: (EI): MH⁺ 311.1763; C₁₉H₂₂N₂O₂ requires MH⁺ 311.1759). The *title compound 217* is also obtained (20% yield) using methyl Z-8-bromo-7-oxooct-2-enoate **196b**.

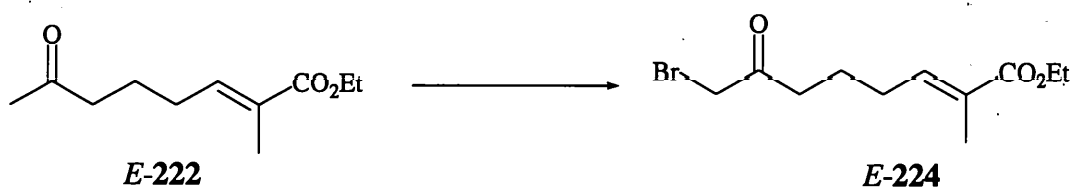
Ethyl *E*-2-methyl-7-oxooct-2-enoate



To a solution of 5-oxohexanal (5.07 g; 43.8 mmol) in dry dichloromethane (50 ml) was added dropwise a solution of ethyl 2-(triphenylphosphoranylidene) propionate¹⁰⁹ **221** in dry dichloromethane (100 ml). The resulting solution was stirred for 8 h, the solvent removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford the *title compound* as a colourless oil (2.8 g; 32%): ν_{max} (film) / cm⁻¹ 2983, 1713, 1650, 1446, 1389, 1261, 1163, 1123, 1088; δ_{H} (300MHz) 1.29 (t, 3H, *J* = 7.1, CO₂CH₂CH₃), 1.73 (quin, 2H, *J* = 7.3, CH₂CH₂CH₂), 1.82 (br. s, 3H, CH=C(CH₃)CO₂CH₃), 2.14 (s, 3H, CH₃COCH₂), 2.20 (q, 2H, *J* = 7.3, CH₂CH=C(CH₃)), 2.45 (t, 2H, *J* = 7.3, CH₃COCH₂), 4.18 (q, 2H, *J* = 7.1, CO₂CH₂CH₃), 6.71 (t, 1H, *J* = 7.5, CH₂CH=C(CH₃)CO₂CH₃); δ_{C} (75MHz) 12.4 (CO₂CH₂CH₃), 14.3 (CH=C(CH₃)CO₂CH₃), 22.5 (CH₂CH₂CH₂), 27.8

(CH₃COCH₂), 29.9 (CH₂CH=CH(CH₃)), 42.8 (CH₃COCH₂), 60.5 (CO₂CH₂CH₃), 129.2 (CH=C(CH₃)CO₂CH₃), 140.9 (CH=C(CH₃)CO₂CH₃), 167.1 (CO₂CH₃), 206.2 (CH₃COCH₂); *m/z* (EI) 199 (MH⁺, 13%), 172 (16%), 152 (51%), 125(15%), 109 (42%), 95 (41%), 84 (71%), 67 (25%), 51 (38%); (Found: (EI) MH⁺ 199.1330; C₁₁H₁₈O₃ requires MH⁺ 199.1334).

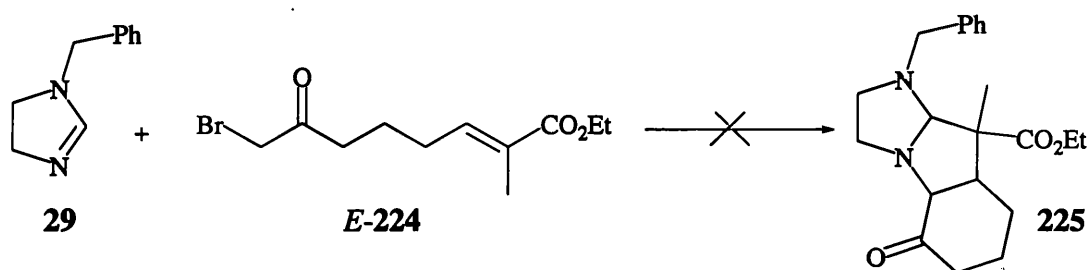
Ethyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate



Prepared as for methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate **196a**, but using ethyl *E*-2-methyl-7-oxooct-2-enoate **222** (1.86 g; 9.39 mmol), LDA (1.2 eq.; 1.12 mmol), chlorotrimethylsilane (5.96 ml; 46.9 mmol), triethylamine (4.74 ml; 46.9 mmol), NaHCO₃ (1.10 g; 13.14 mmol) and N-bromosuccinimide (2.17 g; 12.20 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford the *title compound* as a brown oil (1.16 g; 44%): ν_{\max} (film) / cm⁻¹ 2982, 1713, 1650, 1446, 1393, 1368, 1262, 1184, 1124, 1088; δ_{H} (300MHz) 1.29 (t, 3H, *J* = 7.1, CO₂CH₂CH₃), 1.78 (quin, 2H, *J* = 7.2, CH₂CH₂CH₂); 1.83 (d, 3H, *J* = 1.3, CH=C(CH₃)CO₂Et), 2.21 (q, 2H, *J* = 7.5, CH₂CH₂CH=CH), 2.60 (t, 2H, *J* = 7.1, COCH₂CH₂), 3.87 (s, 2H, BrCH₂CO), 4.19 (q, 2H, *J* = 7.1, CO₂CH₂CH₃), 6.70 (tq, 1H, *J* = 1.3, 6.1, CH₂CH=CH(CH₃)); δ_{C} (75MHz) 12.4 (CO₂CH₂CH₃), 14.3 (CH=CH(CH₃)CO₂Et), 22.6 (CH₂CH₂CH₂), 27.6 (CH₂CH=CH(CH₃); 34.1 (BrCH₂CO), 38.9 (COCH₂CH₂), 60.5 (CO₂CH₂CH₃), 128.9 (CH=CH(CH₃)CO₂Et), 140.4 (CH₂CH=CH(CH₃)), 160.3 (CO₂CH₂CH₃), 201.6

(CH₂COCH₂); *m/z* (CI) 294 (MNH₄⁺, 100%), 277 (5%), 254 (12%), 216 (98%); (EI) 203 (28%), 197 (22%), 169 (62%), 151 (27%), 123 (31%), 112 (30%), 95 (62%), 83 (4%), 82 (27%), 81 (39%), 79 (24%), 67 (33%), 43 (100%); (Found: (CI): MNH₄⁺ 294.0705; C₁₁H₁₇BrO₃ requires MNH₄⁺ 294.0705).

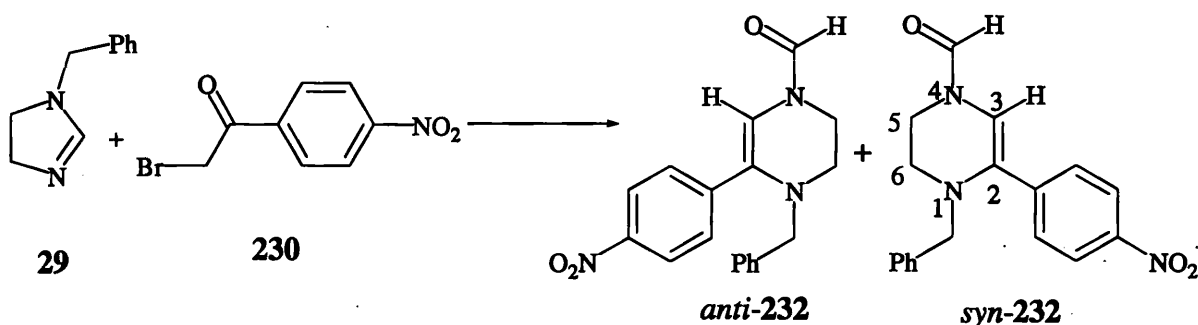
Attempted synthesis of ethyl 1-benzyl-9-methyl-5-oxo-decahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate



Methyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate (0.78 g; 2.83 mmol) in dry THF (5 ml) was added to a solution of 1-benzyl-4,5-dihydroimidazole (0.38 g; 2.36 mmol) in dry THF (15 ml). The solution was refluxed for 2 h and DBU (0.42 ml; 2.83 mmol) was then added dropwise over 4 h. The mixture was refluxed for a further 4h, the reaction flask cooled to RT, the solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (10 : 9 v/v) as eluant but none of the *title compound* was isolated. The data of the isolated product is as follows: ν_{\max} (film) / cm⁻¹ 2979, 1715, 1693, 1455, 1365, 1335, 1262, 1218, 1161, 1116; δ_{H} (300MHz) 1.29 (t, 3H, *J* = 7.3, CO₂CH₂CH₃), 1.52 (m, 1H), 1.76 (m, 1H), 1.82 (s, 3H, CH=C(CH₃)), 1.91 (m, 1H), 2.03 (m, 1H), 2.12 (m, 2H), 2.54 (m, 1H), 3.10 (m, 1H), 3.29 (t, 1H, *J* = 5.0), 3.42 (m, 1H), 3.45 (d, 1H, *J* = 13.4, PhCHH), 3.76 (m, 1H), 3.96 (d, 1H, *J* = 13.4, PhCHH), 4.18 (q, 2H, *J* = 7.3, CO₂CH₂CH₃), 6.73 (tq, 1H, *J* = 1.3, 6.1, CH=C(CH₃)), 7.26

(m, 5H, Ar-H), 9.47 (s, 1H); δ_C (75MHz) 12.4, 14.3, 24.0, 28.4, 29.9, 39.8, 44.9, 58.1, 60.5, 65.4, (128.3, 128.6, 128.7 (3 \times Ar-CH)), 137.2 (Ar-C), 141.2, 162.4, 168.1, 173.3; m/z (CI) 373 (MH^+ , 30%), 345 ($MH^+ - CO$); (Found: (CI): MH^+ 373.2127; $C_{21}H_{28}N_2O_2$ requires MH^+ 373.2126).

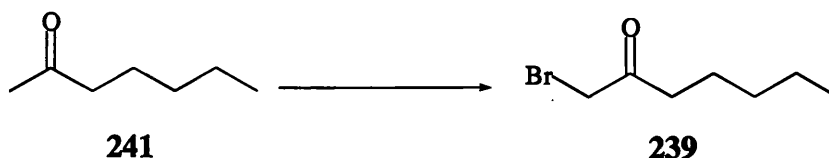
1-Benzyl-4-formyl-2-(4-nitrophenyl)-1,4,5,6-tetrahydropyrazine



Prepared as methyl 1-benzyl-2,3,6a,7,9,9a,9b-octahydro-1H-pyrrolo[1,2,3-de]quinoxaline-6-carboxylate **217** but using 1-benzyl-4,5-dihydroimidazole (0.40 g; 2.50 mmol), commercial 2-bromo-4'-nitroacetophenone **230** (0.67 g; 2.75 mmol) and DBU (0.44 ml; 3.0 mmol). The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (8 : 92 v/v) as eluant to afford the *title compound* as a mixture of rotamers and an orange oil (0.70 g; 87 %): ν_{max} (film) / cm^{-1} 2349, 1683, 1628, 1589, 1515, 1415, 1395, 1343, 1191; δ_H (300MHz) 3.06 (m, 2H, 6- CH_2 of *syn* rotamer), 3.15 (m, 2H, 6- CH_2 of *anti* rotamer), 3.30 (m, 2H, 5- CH_2 of *anti* rotamer), 3.42 (m, 2H, 5- CH_2 of *syn* rotamer), 3.81 (s, 2H, $PhCH_2$), 3.84 (s, 2H, $PhCH_2$ for other rotamer), 6.48 (s, 1H, 3- CH of *syn* rotamer), 6.98 (s, 1H, 3- CH of *anti* rotamer), 7.21-7.32 (m, 9H, Ar-H), 7.66 (m, 2H, $ArNO_2-H$), 7.90 (s, 1H, $N=COH$ of *anti* rotamer), 8.17 (m, 2H, $ArNO_2-H$ for other rotamer), 8.27 (s, 1H, $N=COH$

of *syn* rotamer); δ_C (75MHz) 35.2 (C-5), 40.2 (C-6), 45.2 (C-5 for other rotamer), 46.2 (C-6 for other rotamer), 56.3 (PhCH₂), 56.6 (PhCH₂ for other rotamer), 108.6 (C-3 of *anti* rotamer), 112.2 (C-3 of *syn* rotamer), 124.0 (ArNO₂-CH), 124.1 (ArNO₂-CH), 126.7 (ArNO₂-CH), 127.1 (ArNO₂-CH), 127.7, 127.9, 128.8 (3 \times Ar-CH), 137.1 (Ar-C), 142.2 (ArNO₂-C), 143.1 (C-2 of *anti* rotamer), 147.3 (C-2 of *syn* rotamer), 147.5 (ArNO₂-C), 159.3 (N=CHO of *anti* rotamer), 159.9 (N=CHO of *syn* rotamer); m/z (EI) 324 (MH⁺, 6%), 293 (8%), 174 (8%), 118 (12%), 91 (100%), 65 (28%), 51 (9%); (Found: (EI): M⁺ 323.1268; C₁₈H₁₇N₃O₃ requires M⁺ 323.1270).

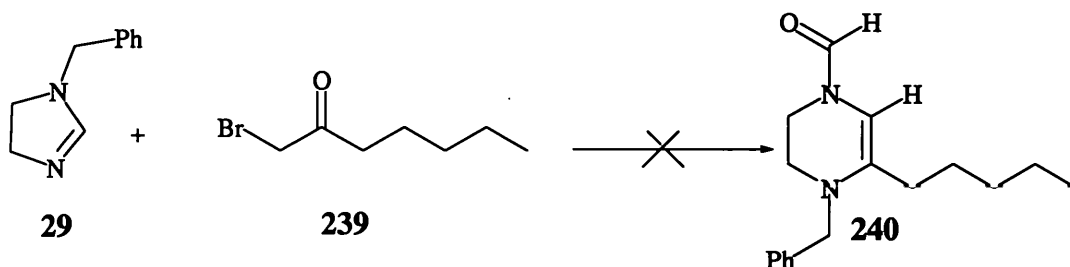
1-bromoheptan-2-one¹²⁴



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a** but using commercial heptan-2-one (4.0 g; 35.0 mmol), LDA (42.0 mmol), prepared from *n*-BuLi (1.6M solution in hexanes; 26.27 ml; 42.0 mmol) and diisopropylamine (6.37 ml; 45.5 mmol), chlorotrimethylsilane (22.21 ml; 175.0 mmol), triethylamine (24.39 ml; 175.0 mmol), NaHCO₃ (4.11 g; 49.0 mmol) and N-bromosuccinimide (8.09 g; 45.5 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7 : 93 v/v) as eluant to afford the *title compound* as a brown oil (2.80 g; 41%): ν_{\max} (film) / cm⁻¹ 2958, 2932, 1718, 1466, 1405; δ_H (300MHz) 0.89 (t, 3H, J = 6.8, CH₃(CH₂)₄CO), 1.31 (m, 4H, CH₃CH₂CH₂), 1.62 (quin, 2H, J = 7.1, COCH₂CH₂CH₂), 2.64 (t, 2H, J = 7.3, BrCOCH₂CH₂), 3.88 (s, 2H,

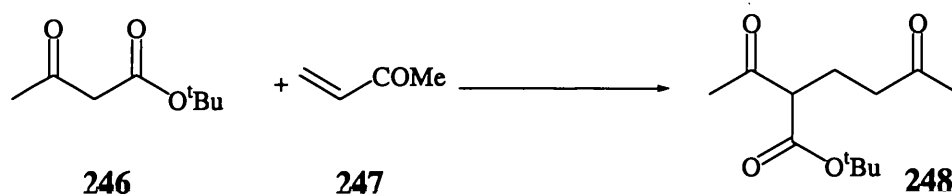
BrCH₂COCH₂); δ_C (75MHz) 13.8 (CH₃(CH₂)₄), 22.4 (CH₃CH₂CH₂CH₂), 23.5 (CH₃CH₂CH₂CH₂), 31.2 (CH₃CH₂CH₂CH₂), 34.3 (BrCH₂COCH₂), 39.8 (BrCH₂COCH₂), 202.3 (BrCH₂COCH₂).

Attempted synthesis of -benzyl-4-formyl-2-(4-pentane)-1,4,5,6-tetrahydropyrazine



Prepared as 1-benzyl-4-formyl-2-(4-nitrophenyl)-1,4,5,6-tetrahydropyrazine **232** but using 1-benzyl-4,5-dihydroimidazole (0.30 g; 1.89 mmol), 1-bromo-heptan-2-one (0.40 g; 2.08 mmol) and DBU (0.33 ml; 2.26 mmol). The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford a compound isolated an oil (0.89 g) and which spectroscopic data is as follows: ν_{\max} (film) / cm⁻¹ 1725, 1695, 1228, 1174; δ_H (300MHz) 0.81 (t, 3H, $J = 6.8$), 1.22 (m, 7H), 1.50 (br. s, 6H), 1.81 (m, 1H), 1.94 (m, 1H), 2.40 (m, 1H), 2.98 (m, 1H), 3.21 (t, 1H, $J = 5.0$), 3.32 (m, 2H), 3.69 (m, 1H), 3.88 (d, 1H, $J = 13.3$, PhCHH), 7.23-7.28 (m, 5H, Ar-H), 9.40 (s, 1H); δ_C (75MHz) 14.0, 22.5, 24.7, 30.2, 31.7, 39.87, 44.9, 58.0, 65.6, (127.56, 128.5, 128.7 (3 \times Ar-CH)), 137.4 (Ar-C), 162.5, 173.6; m/z (CI) 289 (MNH₄⁺, 87%), 261 (96%), 106 (100%).

***tert*-Butyl 2-acetyl-5-oxohexanoate¹¹²**



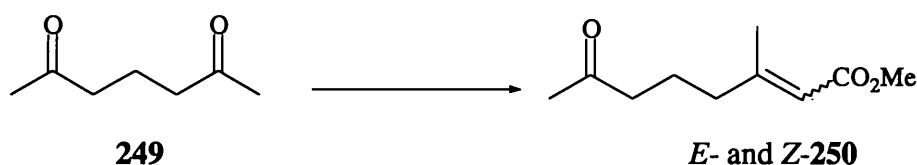
According to the published method,¹¹² to a mixture of cerium (III) chloride heptahydrate (0.94 g; 2.52 mmol) and sodium iodide (0.19 g; 1.26 mmol) was added *tert*-butyl acetoacetate **246** (2.09 ml; 12.6 mmol) followed by but-1-en-3-one **247** (0.93 ml; 13.6 mmol). The resulting mixture was stirred at RT for 8 h until all the starting material was consumed. Dichloromethane (20 ml) was added and the mixture filtered and the residue rinsed with dichloromethane. The combined filtrates were concentrated under reduced pressure and the crude product was purified by silica gel chromatography using ethyl acetate / hexane (4 : 6 v/v) as eluant to afford the title compound a pale yellow oil (2.79 g; 97%): ν_{\max} (film) / cm^{-1} 2979, 1713, 1643, 1422, 1394, 1370, 1254, 1146, 962, 846; δ_{H} (300MHz) 1.46 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 2.03 (m, 2H, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}$), 2.13 (s, 3H, $\text{CH}_3\text{COCHCO}_2^t\text{Bu}$), 2.26 (s, 3H, $\text{CH}_3\text{COCH}_2\text{CH}_2$), 2.48 (t, 2H, $J = 6.9$, $\text{CH}_3\text{COCH}_2\text{CH}_2$), 3.37 (t, 1H, $J = 7.1$, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}$); δ_{C} (75MHz) 22.1 ($\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}$), 27.8 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 28.5 (CH_3CO), 29.6 (CH_3CO), 40.1 ($\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}$), 58.9 ($\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}$), 81.6 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 168.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 202.7 (CH_3CO), 207.3 (CH_3CO); m/z (CI) 246 (MNH_4^+ , 50%), 242 (13%), 225 (5%), 191 (12%), 190 (100%), 176 (14%), 158 (7%), 148 (27%), 146 (62%), 128 (18%), 77 (15%), 61 (8%), 58 (17%); (Found: (CI): MNH_4^+ 246.1698; $\text{C}_{12}\text{H}_{20}\text{O}_4$ requires MNH_4^+ 246.1705).

2,6-heptanedione



tert-Butyl 2-acetyl-5-oxohexanoate **248** (0.66 g; 2.89 mmol) was treated with excess neat trifluoroacetic acid (30 ml) and the resulting red solution was stirred for 30 min at RT. The excess acid was removed under reduced pressure and the residue distilled under reduced pressure to afford the title compound as a colourless oil (0.35 g; 98%): b.p. 92°C / 10 mmHg (lit.,¹²⁵ 94°C / 12 mmHg); ν_{\max} (film) / cm^{-1} 2942, 1714, 1428, 1360, 1171; δ_{H} (300MHz) 1.86 (quin, 2H, $J = 7.1$, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CO}$), 2.14 (s, 6H, $2 \times \text{CH}_3\text{COCH}_2$), 2.46 (t, 4H, $J = 7.1$, $2 \times \text{COCH}_2$); δ_{C} (75MHz) 17.6 ($\text{COCH}_2\text{CH}_2\text{CH}_2\text{CO}$), 29.9 (CH_3CO), 42.4 (CH_3COCH_2), 209.1 ($2 \times \text{CH}_3\text{COCH}_2$).

E- and *Z*-Methyl-3-methyl-7-oxooct-2-enoate



A solution of commercial trimethyl phosphonacetate (3.70 ml; 23 mmol) in dry THF (10 ml) was added dropwise with cooling (ice / water bath) to a suspension of NaH (0.60 g; 25 mmol) in dry THF (30 ml) under nitrogen. The water bath was removed and the mixture stirred at RT for a further 30 min. A solution of 2,6-heptanedione **249** (2.6 g; 20.9 mmol) in dry THF (10 ml) was then added dropwise, and the reaction stirred at RT for a further 10 h. The solvent was removed under reduced pressure and the residue purified by

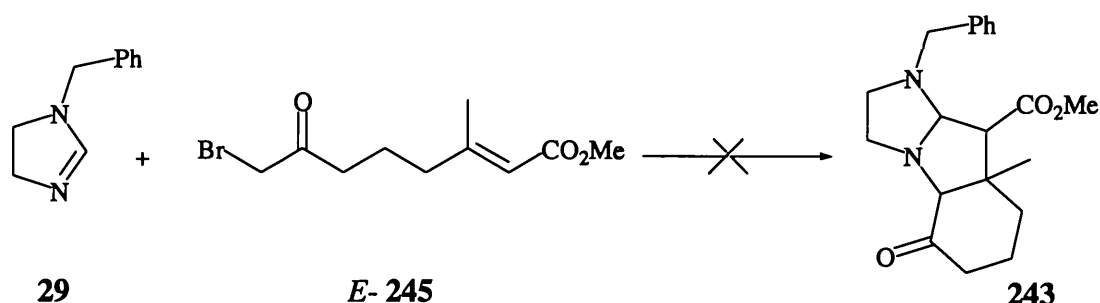
silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title compound* as a yellow oil (1.55 g; 40%), that was an inseparable (50 : 50) mixture of *E*- and *Z*-isomers: ν_{\max} (film) / cm^{-1} 2951, 1718, 1651, 1436, 1363, 1227, 1151, 1085, 1028, 921, 866; δ_{H} (300MHz) 1.77 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.89 (d, 1.5H, $J = 1.3$, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$ for *Z*-isomer), 2.14 (s, 3H, CH_3COCH_2 for both *Z*- and *E*-isomers), 2.16 (d, 1.5H, $J = 1.3$, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$ for *E*-isomer), 2.20 (t, 1H, $J = 7.5$, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$ for *E*-isomer), 2.44 (t, 1H, $J = 7.1$, CH_3COCH_2 for *E*- or *Z*-isomer), 2.49 (t, 1H, $J = 7.1$, CH_3COCH_2 for *E*- or *Z*-isomer), 2.62 (t, 1H, $J = 7.5$, $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$ for *Z*-isomer), 3.67 (s, 1.5H, CO_2CH_3 for *Z*-isomer), 3.69 (s, 1.5H, CO_2CH_3 for *E*-isomer), 5.66 (sext, 0.5H, $J = 1.3$, $\text{C}(\text{CH}_3)=\text{CHCO}_2\text{CH}_3$ for *Z*-isomer), 5.68 (br m, 0.5H, $\text{C}(\text{CH}_3)=\text{CHCO}_2\text{CH}_3$ for *E*-isomer); δ_{C} (75MHz) 21.1, 21.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$ for *E*- and *Z*-isomers), 24.9, 27.9 ($\text{C}(\text{CH}_3)=\text{CHCO}_2\text{Me}$ for *E*- and *Z*-isomers), 29.9, 30.0 (CH_3CO for *E*- and *Z*-isomers), 32.4 (CH_3COCH_2 for *E*- and *Z*-isomers), 42.5, 43.1 ($\text{CH}_2\text{C}(\text{CH}_3)=\text{CHCO}_2\text{Me}$ for *E*- and *Z*-isomers), 50.8, 50.9 (CO_2CH_3 for *E*- and *Z*-isomers), 115.7, 116.2 ($\text{C}(\text{CH}_3)=\text{CHCO}_2\text{CH}_3$ for *E*- and *Z*-isomers), 159.2, 160.0 ($\text{C}(\text{CH}_3)=\text{CHCO}_2\text{Me}$ for *E*- and *Z*-isomers), 166.7, 167.1 (CO_2CH_3 for *E*- and *Z*-isomers), 208.2, 208.7 (CH_3COCH_2 for *E*- and *Z*-isomers); m/z (CI) 202 (MNH_4^+ , 100%), 185 (11%), 172 (13%), 152 (18%), 127 (14%), 109 (38%), 95 (53%), 82 (24%), 79 (7%), 67 (32%), 59 (8%), 55 (20%), 49 (39%), 43 (100%); (Found: (CI): MNH_4^+ 202.1489; $\text{C}_{10}\text{H}_{16}\text{O}_3$ requires MNH_4^+ 202.1443).

Methyl *E*-8-bromo-7-oxo-3-methyl-oct-2-enoate



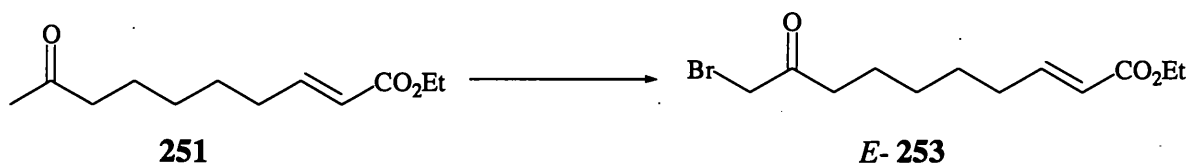
Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a**, using a mixture of *E*- and *Z*-methyl-3-methyl-7-oxooct-2-enoate **250** (0.74 g; 4.02 mmol), LDA (1.2 eq.; 4.8 mmol), chlorotrimethylsilane (2.55 ml; 20.1 mmol), triethylamine (2.80 ml; 20.1 mmol), NaHCO₃ (0.47 g; 5.6 mmol) and N-bromosuccinimide (0.93 g; 5.22 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford the *title compound* as a single isomer and as a brown oil (0.30 g; 30%): ν_{\max} (film) / cm⁻¹ 2950, 1713, 1651, 1436, 1379, 1228, 1155, 1087, 921, 857; δ_{H} (300MHz) 1.70 (quin, 2H, $J = 7.6$, CH₂CH₂CH₂), 1.78 (d, 3H, $J = 1.4$, C(CH₃)=CHCO₂Me), 2.49 (br. t, 2H, $J = 6.6$, CH₂C(CH₃)=CH), 2.59 (t, 2H, $J = 7.3$, COCH₂CH₂), 3.56 (s, 3H, CO₂CH₃), 3.79 (s, 2H, BrCH₂CO), 5.59 (br s, 1H, CH₂C(CH₃)=CHCO₂Me); δ_{C} (75MHz) 22.1 (CH₂CH₂CH₂), 25.1 (C(CH₃)=CH), 32.3 (CH₂CH=CH(CH₃)CO₂Me), 34.4 (BrCH₂CO), 39.3 (COCH₂CH₂), 51.1 (CO₂CH₃), 116.7 (C(CH₃)=CHCO₂Me), 159.7 (CH₂C(CH₃)=CHCO₂Me), 166.9 (CO₂CH₃), 202.0 (CH₂COCH₂); m/z (CI) 280 (MNH₄⁺, 100%), 263 (11%), 258 (13%), 232 (14%), 216 (11%), 203 (12%), 202 (100%), 200 (5%), 185 (16%), 172 (11%); (EI) 151 (42%), 109 (57%), 95 (100%), 82 (44%), 81 (63%), 79 (40%), 67 (68%), 43 (100%); (Found: (CI): MNH₄⁺ 280.0551; C₁₀H₁₅BrO₃ requires MNH₄⁺ 280.0548)

Attempted synthesis of ethyl 1-benzyl-8a-methyl-5-oxo-decahydroimidazo[1,2-*a*]indole-9-carboxylate



Methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate (0.10 g; 0.38 mmol) in dry THF (5 ml) was added to a solution of 1-benzyl-4,5-dihydroimidazole (0.06 g; 0.38 mmol) in dry THF (15 ml). The solution was refluxed for 2 h then DBU (0.07 ml; 0.45 mmol) was added dropwise over 4 h. The mixture was refluxed for a further 4 h, the reaction flask was allowed to cool to RT, the solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (5 : 95 v/v) as eluant but none of the *title compound* was isolated.

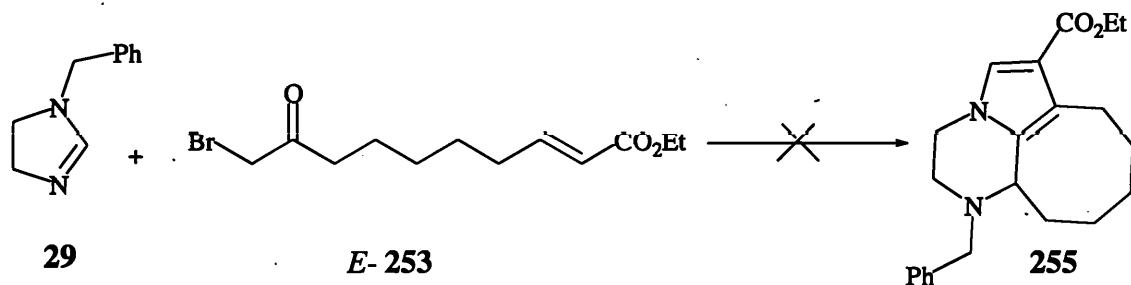
Ethyl *E*-10-bromo-9-oxodec-2-enoate¹²⁶



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a** but using ethyl *E*-9-oxodec-2-enoate **251**¹¹³ (4.0 g; 18.8 mmol), LDA (22.6 mmol), chlorotrimethylsilane (11.93 ml; 94.0 mmol), triethylamine (13.10 ml; 94.0 mmol), NaHCO₃ (2.21 g; 26.32 mmol) and N-bromosuccinimide (4.35 g; 24.4 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl

acetate / hexane (8 : 92 v/v) as eluant to afford the *title compound* as a brown oil (2.0 g; 36%): ν_{\max} (film) / cm^{-1} 2981, 2937, 1713, 1655, 1463, 1393, 1368, 1310, 1269, 1184, 1044, 983; δ_{H} (300MHz) 1.28 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.34 (quin, 2H, $J = 7.2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 1.48 (quin, 2H, $J = 7.2$, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 1.62 (quin, 2H, $J = 7.4$, $\text{COCH}_2\text{CH}_2\text{CH}_2$), 2.20 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.66 (t, 2H, $J = 7.3$, COCH_2CH_2), 3.87 (s, 2H, BrCH_2CO), 4.18 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.81 (dt, 1H, $J = 1.6$, 15.5, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.94 (dt, 1H, $J = 6.9$, 15.5, $\text{CH}=\text{CHCO}_2\text{Et}$); δ_{C} (75MHz) 14.3 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 23.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 27.7 ($\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 28.4 ($\text{COCH}_2\text{CH}_2\text{CH}_2$), 31.9 ($\text{CH}_2\text{CH}=\text{CH}$), 34.2 (BrCH_2CO), 39.6 (COCH_2CH_2), 60.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 121.5 ($\text{CH}=\text{CHCO}_2\text{Et}$), 148.8 ($\text{CH}=\text{CHCO}_2\text{Et}$), 166.7 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 202.0 (CH_2COCH_2); m/z (CI) 308 (MNH_4^+ , 100%), 213 (10%), 202 (8%); (EI) 244 (100%), 217 (21%), 197 (43%), 165 (10%), 137 (17%), 123 (23%), 95 (50%), 81 (54%), 67 (23%), 55 (61%), 43 (100%); (Found: (CI): MNH_4^+ 308.0858; $\text{C}_{12}\text{H}_{19}\text{BrO}_3$ requires MNH_4^+ 308.0861).

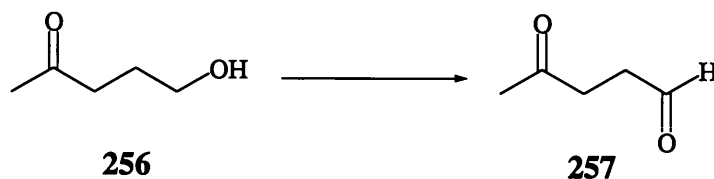
Attempted synthesis Ethyl 5-benzyl-4,5,5a,6,7,8,9,10-octahydro-3H-2a,5-diazacycloocta[cd]indene-1-carboxylate



Prepared as for methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1H-pyrrolo[1,2,3-de]quinoxaline-6-carboxylate **217** but using 1-benzyl-4,5-dihydroimidazole (0.22 g; 1.36

mmol), ethyl *E*-10-bromo-9-oxodec-2-enoate (0.43 g; 1.50 mmol) and DBU (0.25 ml; 1.64 mmol). The solvent was removed under reduced pressure and the subjected to silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) but none of the *title compound* was isolated. The compound isolated was an oil (0.12 g) which spectroscopic data is as follows: ν_{\max} (film) / cm^{-1} 2935, 1720, 1689, 1266, 1217, 909, 733; δ_{H} (300 MHz) 1.28 (t, 3H, $J = 7.3$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.46 (t, 2H, $J = 7.3$), 1.58 (m, 2H), 1.89 (m, 1H), 2.03 (m, 1H), 2.17 (m, 2H), 2.47 (m, 1H), 3.05 (m, 1H), 3.27 (t, 1H, $J = 5.0$), 3.36 (m, 1H), 3.40 (d, 1H, $J = 13.4$, PhCHH), 3.76 (m, 1H), 3.94 (d, 1H, $J = 13.4$, PhCHH), 4.18 (q, 2H, $J = 7.3$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.80 (dt, 1H, $J = 1.6$, 15.6, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.94 (dt, 1H, $J = 6.9$, 15.6, $\text{CH}=\text{CHCO}_2\text{Et}$), 7.32 (m, 5H, Ar-H), 9.47 (s, 1H); δ_{C} (75MHz) 14.3, 24.8, 27.8, 28.9, 30.0, 32.0, 39.8, 44.9, 58.1, 60.1, 65.4, 121.4, (127.6, 128.6, 128.7 ($3 \times \text{Ar-CH}$)), 137.3 (Ar-C), 149.0, 162.4, 166.7, 173.5; m/z (CI) 387 (MH^+ , 60%), 359 ($\text{MH}^+ - \text{CO}$, 90%); (Found: (CI): MH^+ 387.2287; $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2$ requires MH^+ 387.2284).

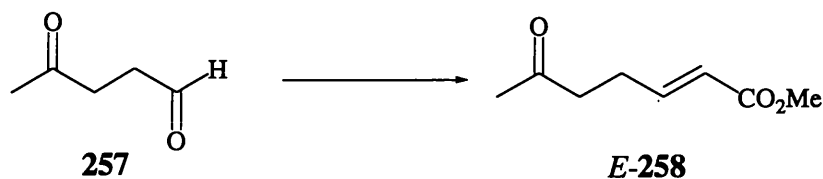
4-Oxopentanal



To an ice-cold suspension of pyridinium chlorochromate (PCC) (31.68 g; 147.0 mmol) in dry dichloromethane (80 ml) and silica (8 g) was added a solution of 5-hydroxypentan-2-one **256** (10.0 g; 98.0 mmol) in dry dichloromethane (50 ml). The resulting mixture was stirred at RT for 2 h then the brown solution was decanted from the

black residues which were then washed using diethyl ether (4 × 300 ml). The combined organic solutions were concentrated by removing the solvent under reduced pressure. The residue was extracted with hexane (3 × 200 ml), the hexane extracts concentrated under reduced pressure and finally distilled to afford the title compound as a colourless oil (1.0 g; 10%): b.p. 86-89°C / 20 mmHg (lit.,¹²⁷ 64-65°C / 11 torr); ν_{\max} (film) / cm^{-1} 3505, 2912, 2844, 1713, 1411, 1369, 1171, 1081, 1030, 968, 880; δ_{H} (300MHz) 2.19 (s, 3H, CH_3COCH_2), 2.76 (s, 4H, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CHO}$), 9.75 (s, 1H, CHO); δ_{C} (75MHz) 29.8 (CH_3COCH_2), 35.5 ($\text{COCH}_2\text{CH}_2\text{CHO}$), 37.4 ($\text{COCH}_2\text{CH}_2\text{CHO}$), 200.4 (CHO), 206.4 (CH_3COCH_2).

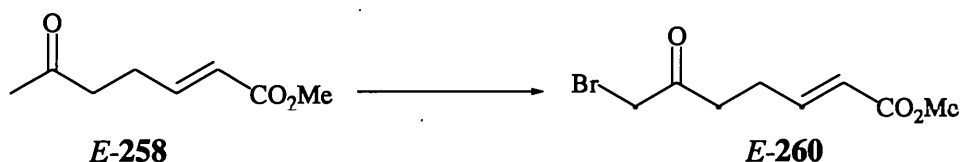
Methyl *E*-6-oxo-hept-2-enoate¹²⁸



Prepared as for methyl *E*-7-oxooct-2-enoate **196a** but using 4-oxopentanal **257** (0.36 g; 3.56 mmol) and methyl (triphenylphosphoranylidene)acetate¹⁰⁶ **210** (1.31 g; 3.90 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (5 : 95 v/v) as eluant to afford the *title compound* as a colourless oil (0.40 g; 72%): ν_{\max} (film) / cm^{-1} 2847, 1723, 1713, 1659, 1462, 1368, 1318, 1276, 1203, 1161, 1097, 1041, 924, 849, 719; δ_{H} (300MHz) 2.14 (s, 3H, CH_3COCH_2), 2.45 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.58 (t, 2H, $J = 6.8$, CH_3COCH_2), 3.69 (s, 3H, CO_2CH_3), 5.80 (dt, 1H, $J = 1.6, 15.6$, $\text{CH}=\text{CHCO}_2\text{Me}$), 6.90 (dt, 1H, $J = 6.8, 15.6$, $\text{CH}=\text{CHCO}_2\text{Me}$); δ_{C} (75MHz) 25.9 ($\text{CH}_2\text{CH}=\text{CHCO}_2\text{Me}$), 29.9 (CH_3COCH_2), 41.4

(CH₃COCH₂), 51.4 (CO₂CH₃), 121.6 (CH=CHCO₂Me), 147.4 (CH=CHCO₂Me), 166.8 (CO₂CH₃), 206.6 (CH₃COCH₂); *m/z* (EI) 156 (M⁺, 98%), 149 (78%), 141 (79%), 135 (34%), 133 (49%), 113 (21%), 81 (39%), 43 (100%); (Found: (EI): MH⁺ 157.0863; C₈H₁₂O₃ requires MH⁺ 157.0864).

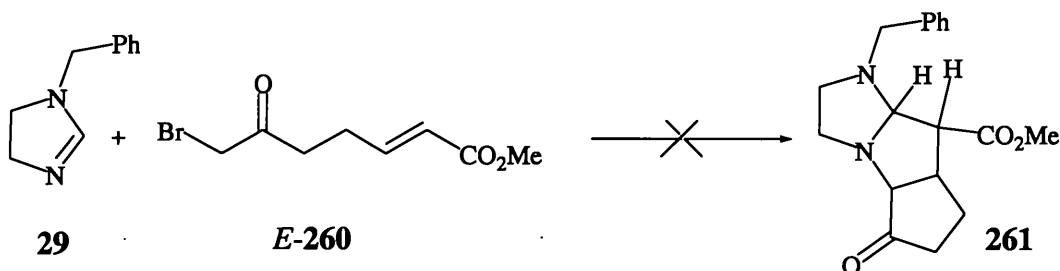
Methyl *E*-7-bromo-6-oxohept-2-enoate



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a** but using methyl *E*-6-oxohept-2-enoate (0.35 g; 2.24 mmol), LDA (2.69 mmol), chlorotrimethylsilane (1.42 ml; 11.2 mmol), prepared from *n*-BuLi (2.5M solution in hexanes; 1.07 ml; 2.69 mmol), triethylamine (1.56 ml; 11.2 mmol), NaHCO₃ (0.22 g; 2.64 mmol) and *N*-bromosuccinimide (0.44 g; 2.44 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title compound* as a brown oil (0.18 g; 34%): ν_{\max} (film) / cm⁻¹ 2840, 1721, 1716, 1665, 1457, 1369, 1312, 1276, 1164, 1091, 1040, 923, 844, 716; δ_{H} (300MHz) 2.38 (m, 2H, CH₂CH=CHCO₂Me), 2.70 (t, 2H, *J* = 7.3, BrCH₂COCH₂CH₂), 3.56 (s, 3H, CO₂CH₃), 3.74 (s, 2H, BrCH₂COCH₂), 5.71 (dt, 1H, *J* = 1.5, 15.6, CH=CHCO₂Me), 6.77 (dt, 1H, *J* = 6.8, 15.6, CH=CHCO₂Me); δ_{C} (75MHz) 25.6 (CH₂CH=CHCO₂Me), 32.9 (BrCH₂COCH₂), 37.6 (BrCH₂COCH₂), 51.4 (CO₂CH₃), 121.9 (CH=CHCO₂Me), 146.5 (CH=CHCO₂Me), 166.6 (CO₂CH₃), 200.3 (BrCH₂COCH₂); *m/z*

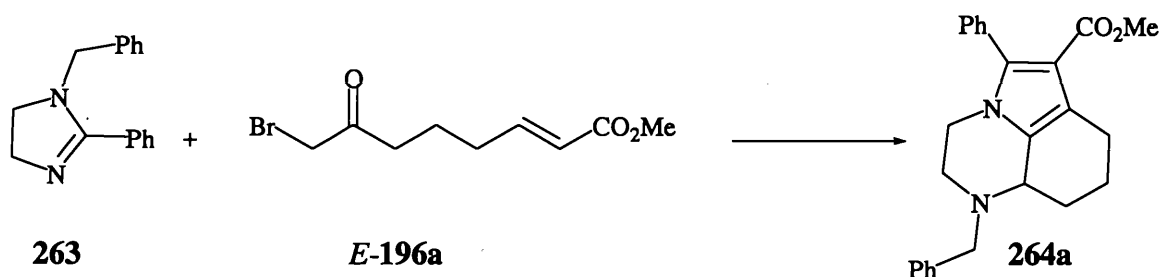
(CI) 174 (MNH_4^+ , 100%), (EI) 156 (100%), 149 (75%), 141 (75%), 133 (48%), 81 (34%), 43 (100%); (Found: (EI): MNH_4^+ 252.0232; $\text{C}_8\text{H}_{12}\text{O}_3$ requires MNH_4^+ 252.0235).

Attempted synthesis of methyl 1-benzyl-5-oxo-decahydro-1,4-diazacyclopenta[1,2-*a*]pentalene-8-carboxylate



Prepared as for methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **217** but using 1-benzyl-4,5-dihydroimidazole (0.07 g; 0.43 mmol), methyl *E*-7-bromo-6-oxohept-2-enoate (0.11 g; 0.47 mmol) and DBU (0.08 ml; 0.51 mmol). The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant but none of the *title compound* was isolated.

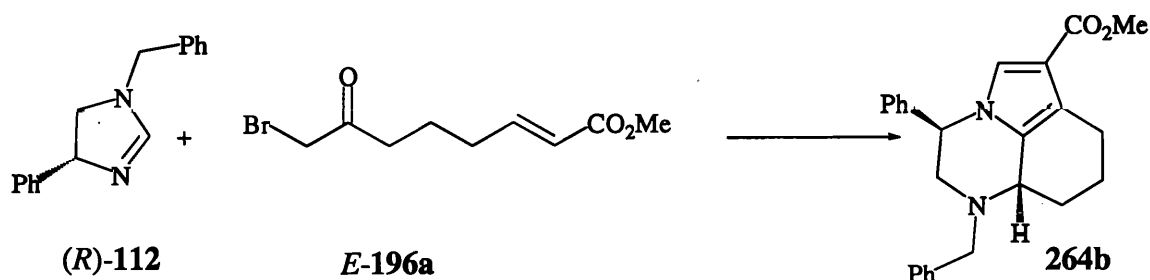
Methyl 6-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate



To a solution of 1-benzyl-2-phenyl-4,5-dihydroimidazole (0.23 g; 1.0 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of methyl *E*-8-bromo-

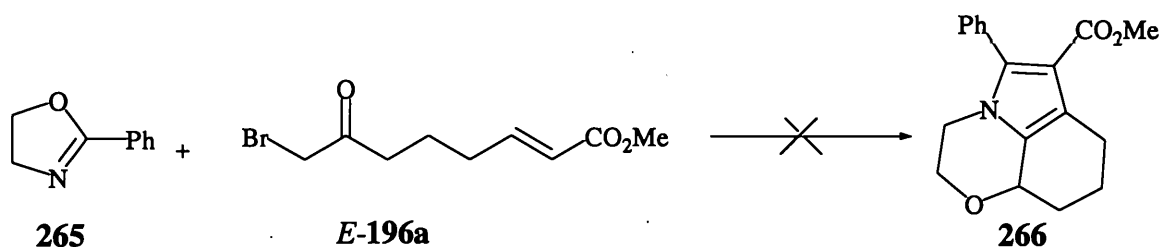
7-oxooct-2-enoate (0.27 g; 1.1 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.15 ml; 1.2 mmol) was added dropwise over 4 h. The reaction was kept at reflux for a further 4 h, cooled, the solvent evaporated under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (3 : 7 v/v) as eluant to afford the *title compound* as a white solid (0.13 g; 33%). Recrystallisation from methanol / hexane gave white needles for X-ray crystallographic analysis: m.p. 148-150°C; ν_{\max} (nujol) / cm^{-1} 2932, 2857, 1694, 1489, 1466, 1382, 1348, 1264, 1193, 1170, 1086, 911, 736, 701; δ_{H} (300MHz) 1.55 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.80 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.14 (m, 1H, 8-CHH), 2.33 (m, 1H, 9-CHH), 2.45 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 2-CHH), 2.72 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.94 (m, 2H, 7-CHH and 2-CHH), 3.12 (d, 1H, $J = 13.3$, PhCH_2), 3.34 (br. d, 1H, $J = 10.6$, 9a-CH), 3.52 (m, 2H, 3-CH₂), 3.60 (s, 3H, CO_2CH_3), 4.26 (d, 1H, $J = 13.3$, PhCH_2), 7.26-7.32 (m, 10H, Ar-H); δ_{C} (75MHz) 22.5, 23.0 (C-8 and C-7), 28.0 (C-9), 44.2 (C-2), 49.9 (C-3), 50.4 (CO_2CH_3), 57.3 (PhCH_2), 59.7 (C-9a), 111.2 (C-6a), 117.5 (C-6), 127.1, 127.8, 127.9, 128.3, 128.5, 128.9 ($6 \times \text{Ar-CH}$), 130.4 (C-9b), 132.0 (C-5), 136.7, 138.3 ($2 \times \text{Ar-C}$), 165.9 (CO_2CH_3); m/z (EI) 387 (MH^+ , 21%), 359 (26%), 358 (98%), 267 (54%), 237 (22%), 207 (11%), 180 (12%), 167 (8%), 91 (100%), 65 (8%), 49 (4%); (Found: (EI): MH^+ 387.2077; $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2$ requires MH^+ 387.2072)

Methyl (3R,9S)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1H-pyrrolo[1,2,3-de]quinoxaline-6-carboxylate



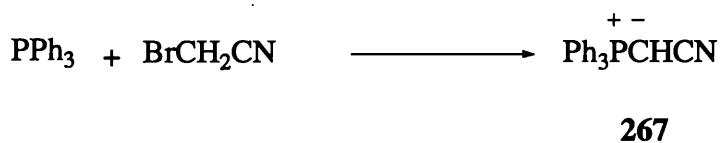
To a solution of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole (0.20 g; 0.88 mmol)⁸⁵ in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of methyl *E*-8-bromo-7-oxooct-2-enoate (0.24 g; 0.96 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.15 ml; 0.10 mmol) was added dropwise over 4 h. The reaction was kept at reflux for a further 4, cooled, the solvent evaporated under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title compound* as a white solid (0.10 g; 30%). Recrystallisation from methanol / hexane gave white needles for X-ray crystallographic analysis: m.p. 176-176°C; ($[\alpha]_D^{20} = +32.01$; $c = 0.345$; DCM); ν_{\max} (nujol) / cm^{-1} 2945, 1704, 1631, 1518, 1495, 1454, 1358, 1334, 1243, 1208, 1092, 892, 737, 701; δ_H (300MHz) 1.53 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.82 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.15 (m, 1H, 8-CHH), 2.35 (m, 1H, 9-CHH), 2.40 (dd, 1H, $J = 4.9, 12.4$, 2-CHH), 2.71 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.92 (dd, 1H, $J = 6.4, 16.8$, 7-CHH), 3.08 (dd, 1H, $J = 4.9, 12.4$, 2-CHH), 3.12 (d, 1H, $J = 13.3$, PhCH₂), 3.45 (br. d, 1H, $J = 10.6$, 9a-CH), 3.72 (s, 3H, CO₂CH₃), 4.24 (d, 1H, $J = 13.3$, PhCH₂), 4.90 (dd, 1H, $J = 4.9, 12.4$, 3-CH), 6.86 (s, 1H, 5-CH), 7.28-7.31 (m, 10H, Ar-H); δ_C (75MHz) 22.3, 22.6 (C-8 and C-7), 28.1 (C-9), 50.6 (CO₂CH₃), 57.1 (PhCH₂), 59.1 (C-2), 59.5 (C-9a), 60.3 (C-3), 114.1 (C-6a), 117.1 (C-6), 124.3 (C-5), 127.2, 127.7, 128.4, 128.5, 128.7, 128.9 (6 × Ar-CH), 130.2 (C-9b), 138.2, 138.6 (2 × Ar-C), 165.8 (CO₂CH₃); m/z (EI) 387 (MH⁺, 20%), 359 (27%), 358 (92%), 268 (20%), 267 (100%), 238 (7%), 206 (8%), 91 (100%), 65 (6%); (Found: C, 76.87; H, 6.66; N, 7.00%; EI): MH⁺ 387.2069; C₂₅H₂₆N₂O₂·0.25 MeOH requires C, 76.88; H, 6.90; N, 7.10%; MH⁺ 387.2072).

Attempted synthesis of methyl 2,3,7,8,9,9a-hexahydro-1-oxa-3a-aza-5-phenylacenaphthylene-6-carboxylate

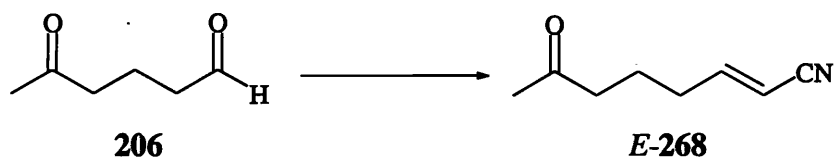


Prepared as for methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **217** but using 2-phenyl-2-oxazoline **265** (0.10 g; 0.72 mmol), methyl *E*-8-bromo-7-oxooct-2-enoate (0.19 g; 0.79 mmol) and DBU (0.12 ml; 0.79 mmol). The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (2 : 8 v/v) as eluant but none of the *title compound* was isolated. Both starting materials, 2-phenyl-2-oxazoline **265** and methyl *E*-8-bromo-7-oxooct-2-enoate **196a** were recovered in 85% and 15%, respectively.

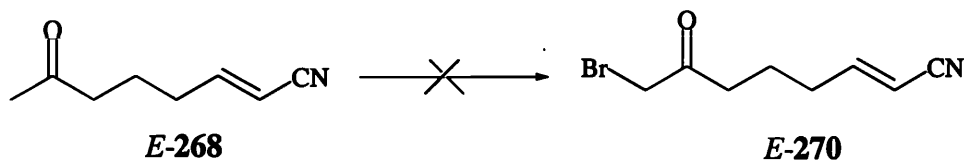
Cyano(methylenetriphenyl)phosphorane¹⁰³



Prepared as for methyl (triphenylphosphoranylidene)acetate **210**, using triphenyl phosphine (20 g; 76.0 mmol) and chloroacetonitrile (9.70 ml; 152.0 mmol) to afford the title compound as a white solid (20.1 g; 88%): m.p. 248-250°C (lit.,¹²⁹ 246°C).

***E*-7-oxo-oct-2-ene-nitrile¹³⁰**

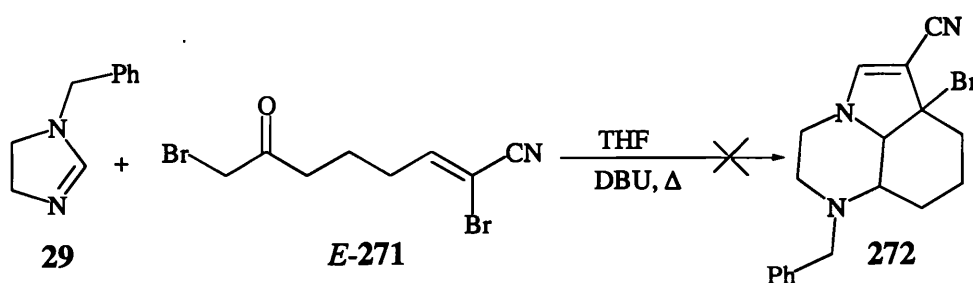
Prepared as for methyl *E*-7-oxooct-2-enoate **196a**, using crude 5-oxohexanal (4.72 g; 41 mmol) and cyano(methylenetriphenyl)phosphorane (14.9 g; 49.6 mmol) **267**. The residue was purified by silica gel column chromatography using ethyl acetate / hexane (15 : 85 v/v) as eluant to afford the *title compound* as a colourless oil (3.0 g; 53%): ν_{\max} (film) / cm^{-1} 2943, 2223, 1714, 1633, 1414, 1369, 1161, 975, 736; δ_{H} (300MHz) 1.72 (quin, 2H, $J = 7.1$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.13 (s, 3H, CH_3CO), 2.22 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCN}$), 2.38 (t, 2H, $J = 7.4$, COCH_2), 5.40 (dt, 1H, $J = 1.5$, 15.6, $\text{CH}=\text{CHCN}$), 6.78 (dt, 1H, $J = 6.8$, 15.6, $\text{CH}=\text{CHCN}$); δ_{C} (75MHz) 21.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 30.1 (CH_3COCH_2), 31.2 ($\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 42.2 (CH_3COCH_2), 100.4 ($\text{CH}=\text{CHCN}$), 117.3 ($\text{CH}=\text{CHCN}$), 154.1 ($\text{CH}=\text{CHCN}$), 207.5 (CH_3COCH_2); m/z (CI) 155 (MNH_4^+ , 100%), 132 (4%), 94 (12%), 84 (3%), 80 (19%), 73 (6%), 67 (17%), 58 (53%), 49 (6%), 43 (100%); (Found: (CI): MNH_4^+ 155.1183; $\text{C}_8\text{H}_{11}\text{NO}$ requires MNH_4^+ 155.1184).

Attempted synthesis of *E*-8-bromo-7-oxo-oct-2-ene-nitrile

Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a**, using *E*-7-oxooct-2-enenitrile (1.40 g; 10.2 mmol), freshly prepared LDA (1.20 eq.; 12.16 mmol), prepared from *n*-BuLi (1.6M solution in hexanes; 7.66 ml; 12.26 mmol) and diisopropylamine (1.85

ml; 13.2 mmol), chlorotrimethylsilane (6.47 ml; 51.0 mmol), triethylamine (7.10 ml; 51.0 mmol), NaHCO₃ (1.19 g; 11.3 mmol) and N-bromosuccinimide (2.36 g; 13.26 mmol). The solvent was removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate / hexane (15 : 85 v/v) but the none of the *title compound* was isolated. The compound *E*-2,8-dibromo-7-oxo-oct-2-ene-nitrile **271** was isolated as a brown oil (0.35 g; 12%): ν_{max} (film) / cm⁻¹ 2958, 2202, 1718, 1589, 1409, 1369, 1254, 846, 763, 699, 666; δ_{H} (300MHz) 1.47 (quin, 2H, $J = 7.8$, COCH₂CH₂CH₂), 2.07 (q, 2H, $J = 7.8$, CH₂CH₂CH), 2.42 (t, 2H, $J = 7.0$, BrCH₂COCH₂), 3.58 (s, 2H, BrCH₂CO), 6.75 (t, 1H, $J = 7.8$, CH₂CH₂CH); δ_{C} (75MHz) 22.7 (COCH₂CH₂CH₂), 31.7 (CH₂CH₂CH), 34.5 (BrCH₂CO), 39.1 (BrCH₂COCH₂), 116.5 (C=N), 121.4 (CH=C(Br)CN), 165.0 (CH=C(Br)CN), 201.8 (BrCH₂CO). The low and high-resolution mass spectroscopic analysis did not show the presence of either M⁺ or MH⁺ for **271**.

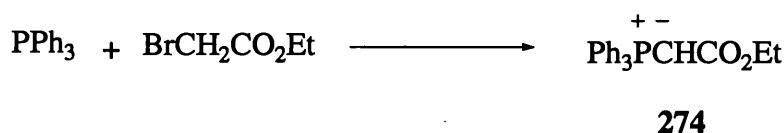
Attempted synthesis of 1-benzyl-6a-bromo-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-cyanate



Prepared as for methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate **217** but using 1-benzyl-4,5-dihydroimidazole **29** (0.04 g; 0.27 mmol), *E*-2,8-dibromo-7-oxo-oct-2-ene-nitrile **271** (0.09 g; 0.32 mmol) and DBU (0.04 ml; 0.32 mmol). The solvent was removed under reduced pressure and the residue

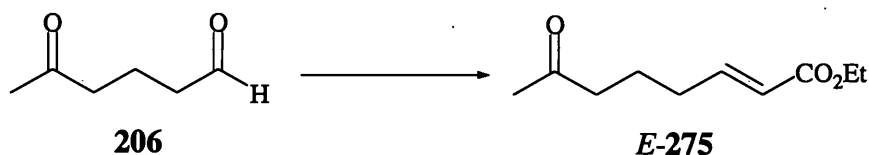
subjected to silica gel column chromatography using ethyl acetate / hexane (2 : 8 v/v) as eluant but none of the *title compound* was isolated. Only unchanged starting material **29** was isolated in virtually quantitative yield.

Ethyl (triphenylphosphoranylidene)acetate¹⁰³



Prepared as for methyl (triphenylphosphoranylidene)acetate **210**, using triphenyl phosphine (25 g; 95.3 mmol) and ethyl bromoacetate (11.62 ml; 104.8 mmol) to afford the title compound as a white solid (28 g; 84%): m.p. 118-118°C (lit.,¹²³ 116-117°C).

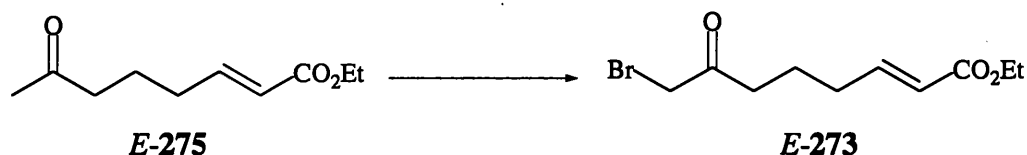
Ethyl *E*-7-oxooct-2-enoate¹³¹



Prepared as for methyl *E*-7-oxooct-2-enoate **196a**, but using 5-oxo-hexanal (6.65 g; 58.3 mmol) and ethyl (triphenylphosphoranylidene)acetate (22.31 g; 64.1 mmol) **274**. The residue was purified by silica gel column chromatography using ethyl acetate / hexane (8 : 92 v/v) as eluant to afford the *title compound* as a colourless oil (6.40 g; 59%): ν_{max} (film) / cm^{-1} 2982, 1718, 1655, 1447, 1368, 1270, 1191, 1045, 985; δ_{H} (300MHz) 1.28 (t, 3H, $J =$

7.1, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.75 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.14 (s, 3H, CH_3CO), 2.20 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCO}_2\text{Et}$), 2.46 (t, 2H, $J = 7.3$, CH_3COCH_2), 4.19 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.82 (dt, 1H, $J = 1.6$, 15.5, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.92 (dt, 1H, $J = 6.9$, 15.5, $\text{CH}=\text{CHCO}_2\text{Et}$); δ_{C} (75MHz) 14.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 21.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 29.9 (CH_3COCH_2), 31.2 ($\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 42.5 (CH_3COCH_2), 60.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 122.0 ($\text{CH}=\text{CHCO}_2\text{Et}$), 147.9 ($\text{CH}=\text{CHCO}_2\text{Et}$), 166.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 208.1 (CH_3COCH_2); m/z (CI) 202 (MNH_4^+ , 100%), 185 (10%), 158 (12%); (EI) 185 (MH^+ , 10%), 139 (44%), 138 (70%), 127 (23%), 114 (42%), 110 (28%), 99 (93%), 95 (71%), 86 (38%), 81 (75%), 68 (53%), 58 (49%), 43 (100%); (Found: (CI): MNH_4^+ 202.1443, $\text{C}_{10}\text{H}_{16}\text{O}_3$ requires MNH_4^+ 202.1443).

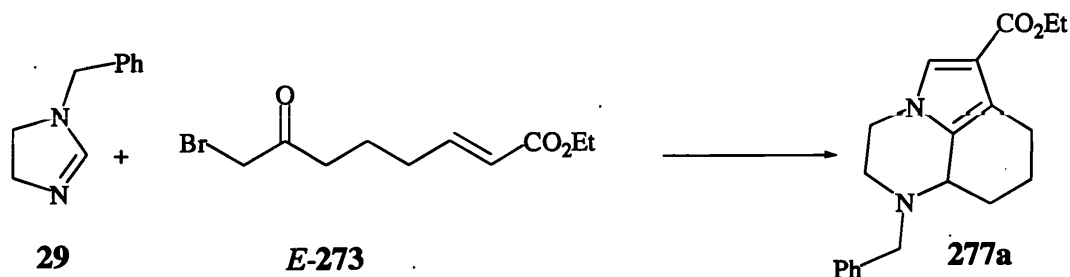
Ethyl *E*-8-bromo-7-oxooct-2-enoate



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a** but using ethyl *E*-7-oxooct-2-enoate (3.85 g; 20.9 mmol), LDA (19.42 ml; 25 mmol), prepared from *n*-BuLi (1.6M solution in hexanes; 15.62 ml; 25 mmol) and diisopropylamine (3.81 ml; 27 mmol), chlorotrimethylsilane (13.26 ml; 104.5 mmol), triethylamine (14.56 ml; 104.5 mmol), NaHCO_3 (2.45 g; 29.2 mmol) and *N*-bromosuccinimide (4.83 g; 27.2 mmol). The residue was purified by silica gel column chromatography using ethyl acetate / hexane (9 : 91 v/v) as eluant to afford the *title compound* as a brown oil (2.30 g; 41%): ν_{max} (film) / cm^{-1} 2980, 1714, 1655, 1394, 1271, 1186, 1096, 1042, 981, 843; δ_{H} (300MHz) 1.19 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.70 (quin, 2H, $J = 7.2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 2.23 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$),

2.54 (t, 2H, $J = 7.3$, CH_3COCH_2), 3.76 (s, 2H, BrCH_2CO), 4.08 (q, 2H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.73 (dt, 1H, $J = 1.6$, 15.6, $\text{CH}=\text{CHCO}_2\text{Et}$), 6.80 (dt, 1H, $J = 6.9$, 15.6, $\text{CH}=\text{CHCO}_2\text{Et}$); δ_{C} (75MHz) 14.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 22.1 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 31.5 ($\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$), 34.2 (BrCH_2CO); 38.9 (COCH_2CH_2), 60.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 122.5 ($\text{CH}=\text{CHCO}_2\text{Et}$), 148.2 ($\text{CH}=\text{CHCO}_2\text{Et}$), 166.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 201.6 (BrCH_2CO); m/z (CI) 280 (MNH_4^+ , 100%), 266 (23%), 254 (31%), 242 (18%), 240 (32%), 237 (26%), 204 (19%), 202 (100%), 158 (28%); (EI) 263 (MH^+ , 12%), 191 (7%), 169 (5%), 137 (38%), 123 (24%), 109 (18%), 99 (31%), 95 (55%), 85 (46%), 68 (33%), 55 (61%), 43 (100%); (Found: (CI): MNH_4^+ 280.0550; $\text{C}_{10}\text{H}_{15}\text{BrO}_3$ requires MNH_4^+ 280.0548).

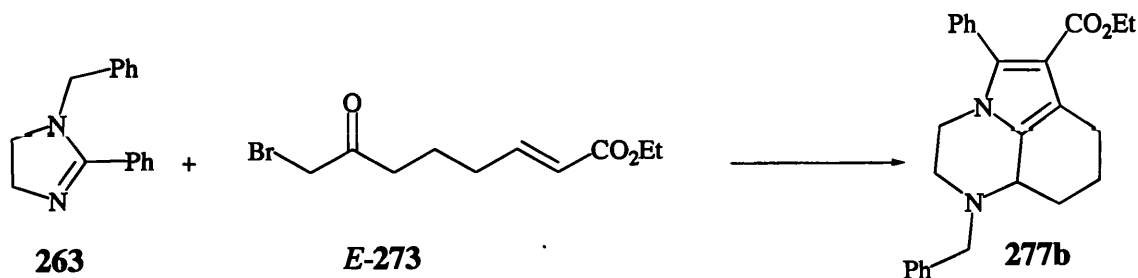
Ethyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1H-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate



To a solution of 1-benzyl-4,5-dihydroimidazole (0.16 g; 1.03 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of ethyl *E*-8-bromo-7-oxooct-2-enoate (0.30 g; 1.14 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.186 ml; 1.12 mmol) was added dropwise over 4 h. The reaction was kept at reflux for a further 4 h, cooled, the solvent removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford the *title compound* as a white solid (0.10 g; 30%). Recrystallisation from

methanol / hexane gave white needles for X-ray crystallographic analysis: m.p. 122-123°C; ν_{\max} (nujol) / cm^{-1} 2942, 2880, 1730, 1698, 1530, 1662, 1175, 1098, 1054, 918, 730; δ_{H} (300MHz) 1.19 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.35 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.65 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.02 (m, 1H, 8-CHH), 2.17 (m, 1H, 9-CHH), 2.36 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 2-CHH), 2.54 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.75 (dd, 1H, $J = 6.4, 16.8$, 7-CHH), 2.90 (ddd, 1H, $J = 2.3, 3.9, 12.5$, 2-CHH), 3.01 (d, 1H, $J = 13.2$, PhCHH), 3.16 (br. d, 1H, $J = 10.6$, 9a-CH), 3.72 (m, 2H, 3-CH₂), 4.12 (m, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$ and PhCHH), 7.02 (s, 1H, 5-CH), 7.18-7.25 (m, 5H, Ar-H); δ_{C} (75MHz) 14.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 22.5, 22.6 (C-8 and C-7), 27.9 (C-9), 45.0 (C-2), 49.8 (C-3), 57.3 (PhCH₂), 59.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 59.7 (C-9a), 114.2 (C-6a), 117.0 (C-6), 124.3 (C-5), 127.3, 128.4, 129.0 ($3 \times \text{Ar-CH}$), 129.3 (C-9b), 138.5 (Ar-C), 165.6 ($\text{CO}_2\text{CH}_2\text{CH}_3$); m/z (EI) 325 (MH^+ , 100%), 235 (15%), 233 (12%), 106 (7%), 91 (100%), 65 (18%), 52 (38%); (Found: C, 73.18; H, 7.35; N, 8.18%; (EI): MH^+ 325.1921, $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2 \cdot 0.25 \text{ MeOH}$ requires C, 73.16; H, 7.58; N, 8.43%; MH^+ 325.1916).

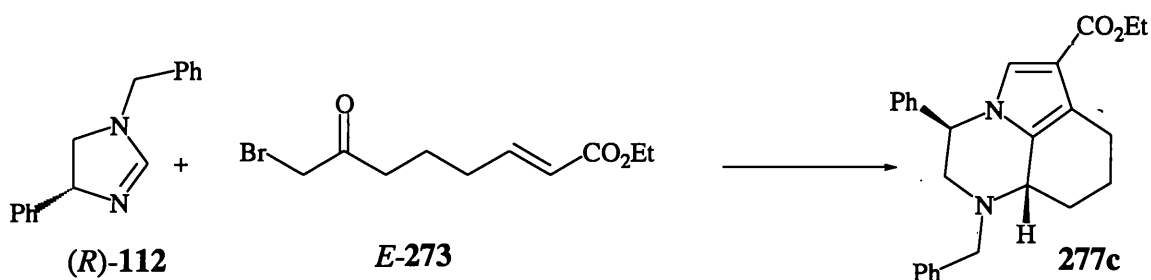
Ethyl 6-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1H-pyrrolo[1,2,3-de]quinoxaline-6-carboxylate



To a solution of 1-benzyl-2-phenyl-4,5-dihydroimidazole (0.20 g; 0.86 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of ethyl E-8-

bromo-7-oxooct-2-enoate (0.25 g; 0.95 mmol) in dry THF (5 ml). The resulting solution was taken and kept at reflux for 2 h. DBU (0.15 ml; 1.03 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The reaction was cooled, the solvent removed under residue and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title compound* as a white solid (0.11 g; 31%): m.p. 124-125°C; ν_{\max} (nujol) / cm^{-1} 2932, 2857, 1694, 1489, 1414, 1382, 1348, 1264, 1170, 1148, 1067, 773, 736; δ_{H} (300MHz) 1.08 (t, 3H, $J = 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.50 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.78 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.17 (m, 1H, 8-CHH), 2.32 (m, 1H, 9-CHH), 2.45 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 2-CHH), 2.73 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.94 (m, 2H, 7-CHH and 2-CHH), 3.12 (d, 1H, $J = 13.3$, PhCH_2), 3.34 (br. d, 1H, $J = 10.6$, 9a-CH), 3.53 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 3-CHH), 3.63 (ddd, 1H, $J = 2.3, 3.9, 12.5$, 3-CHH), 4.07 (q, 2H, $J = 1.29, 7.1$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.26 (d, 1H, $J = 13.3$, PhCH_2), 7.28-7.31 (m, 10H, Ar-H); δ_{C} (75MHz) 14.1 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 22.5, 22.9 (C-8 and C-7), 28.0 (C-9), 44.2 (C-2), 49.9 (C-3), 57.3 (PhCH_2), 58.9 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 59.7 (C-9a), 112.8 (C-6a), 117.5 (C-6), 127.1, 127.7, 17.8, 128.3, 128.5, 128.9 ($6 \times \text{Ar-CH}$), 130.5 (C-9b), 132.1 (C-5), 138.4 ($2 \times \text{Ar-C}$), 165.4 ($\text{CO}_2\text{CH}_2\text{CH}_3$); m/z (EI) 401 (MH^+ , 25%), 373 (22%), 372 (100%), 299 (23%), 281 (23%), 253 (34%), 237 (31%), 207 (31%), 178 (28%), 91 (100%), 55 (35%), 43 (68%); (Found: (EI): MH^+ 401.2234; $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_2$ requires MH^+ 401.2229).

Ethyl (3*R*,9*S*)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate



To a solution of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole (0.20 g; 0.86 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of ethyl *E*-8-bromo-7-oxooct-2-enoate (0.25 g; 0.95 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.15 ml; 0.10 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The reaction was cooled, the solvent removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title compound* as a yellow oil (0.10 g; 30%): ($[\alpha]_{\text{D}}^{20} = +47.12$; $c = 2$; DCM); ν_{max} (film) / cm^{-1} 2858, 2362, 2341, 1716, 1699, 1577, 1419, 1359, 1334, 1244, 1197, 1186, 1094, 1064, 853, 701; δ_{H} (300MHz) 1.26 (t, 3H, $J = 7.0$, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.49 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-*CHH*), 1.82 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-*CHH*), 2.13 (m, 1H, 8-*CHH*), 2.37 (m, 1H, 9-*CHH*), 2.42 (dd, 1H, $J = 4.9, 12.4$, 2-*CHH*), 2.72 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-*CHH*), 2.94 (dd, 1H, $J = 6.4, 16.8$, 7-*CHH*), 3.09 (dd, 1H, $J = 4.9, 12.4$, 2-*CHH*), 3.16 (d, 1H, $J = 13.2$, Ph*CHH*), 3.45 (br. d, 1H, $J = 10.6$, 9a-*CH*), 4.15-4.27 (q, 2H, $J = 7.0$, $\text{CO}_2\text{CH}_2\text{CH}_3$ and d, 1H, $J = 13.2$, Ph*CHH*), 4.88 (dd, 1H, $J = 4.9, 12.4$, 3-*CH*), 6.87 (s, 1H, 5-*CH*), 7.31-7.35 (m, 10H, Ar-*H*); δ_{C} (75MHz) 14.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 22.3, 22.5 (C-8 and C-7), 29.5 (C-9), 52.7 (C-2), 57.0 (Ph CH_2), 59.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 59.5 (C-9a), 60.3 (C-3), 114.7 (C-6a), 117.2 (C-6),

124.2 (C-5), 127.1, 127.6, 128.3, 128.4, 128.7, 128.9 (6 × Ar-CH), 130.6 (C-9b), 138.2, 128.62 (2 × Ar-C), 168.5 (CO₂CH₂CH₃); *m/z* (EI) 401 (MH⁺, 23%), 372 (88%), 300 (41%), 281 (100%), 252 (60%), 208 (36%), 206 (44%), 180 (34%), 149 (53%), 91 (100%), 55 (30%), 43 (59%); (Found: (EI): MH⁺ 401.2229; C₂₆H₂₈N₂O₂ requires MH⁺ 401.2229).

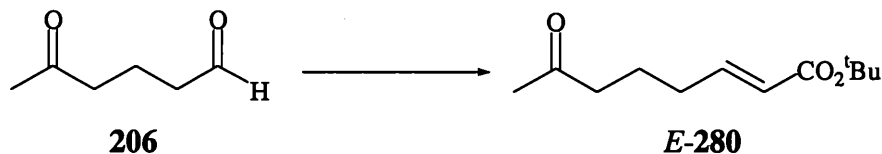
***tert*-Butyl (triphenylphosphoranylidene) acetate¹⁰⁶**



279

Prepared as for methyl (triphenylphosphoranylidene)acetate **210**, using triphenyl phosphine (25 g; 95.3 mmol) and *tert*-butyl bromoacetate (18.59 ml; 114.0 mmol) to afford the title compound as a white solid (32 g; 89%): m.p. 156-157°C (lit.,¹³² 154-155°C); *v*_{max} (nujol) / cm⁻¹ 3000, 2980, 1605, 1436, 1363, 1161; δ_H (300MHz) 1.26 (s, 9H, CO₂C(CH₃)₃), 2.78 (d, 1H, *J* = 21.5, Ph₃PCH), 7.20-7.46 (m, 15H, Ar-*H*).

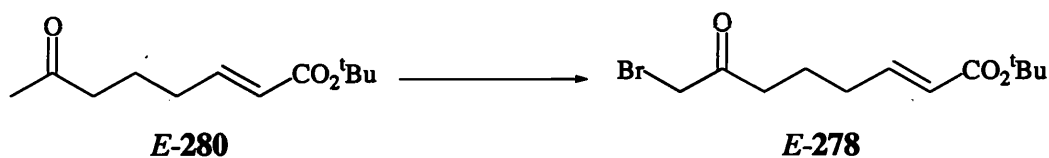
***tert*-Butyl *E*-7-oxooct-2-enoate**



Prepared as for methyl *E*-7-oxooct-2-enoate **196a**, but using 5-oxohexanal (4.83 g; 42.0 mmol) and *tert*-butyl (triphenylphosphoranylidene)acetate (17.54 g; 46.6 mmol) **279**. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (8 : 92 v/v) as eluant to afford the *title*

compound as a colourless oil (5.2 g; 58%): ν_{\max} (film) / cm^{-1} 2979, 1713, 1654, 1478, 1393, 1368, 1317, 1293, 1257, 1223, 1162, 984; δ_{H} (300MHz) 1.48 (s, 9H, $\text{CO}_2(\text{CH}_3)_3$), 1.73 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.14 (s, 3H, CH_3CO), 2.20 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 2.45 (t, 2H, $J = 7.3$, CH_3COCH_2), 5.74 (dt, 1H, $J = 1.5$, 15.5, $\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 6.80 (dt, 1H, $J = 7.0$, 15.5, $\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$); δ_{C} (75MHz) 21.9 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 28.1 ($\text{CH}=\text{CHCO}_2\text{C}(\text{CH}_3)_3$), 29.9 ($\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 31.1 (CH_3COCH_2), 42.6 (COCH_2CH_2), 80.2 ($\text{CH}=\text{CHCO}_2\text{C}(\text{CH}_3)_3$), 123.7 ($\text{CH}=\text{CHCO}_2^t\text{Bu}$), 146.7 ($\text{CH}=\text{CHCO}_2^t\text{Bu}$), 167.1 (CO_2^tBu), 206.4 (CH_3COCH_2); m/z (CI) 230 (MNH_4^+ , 68%), 174 (100%); (EI) 156 (8%), 139 (8%), 138 (22%), 120 (3%), 111 (11%), 95 (16%), 84 (7%), 81 (18%), 68 (18%), 57 (80%), 43 (100%); (Found: (CI): MNH_4^+ 230.1752; $\text{C}_{12}\text{H}_{20}\text{O}_3$ requires MNH_4^+ 230.1756).

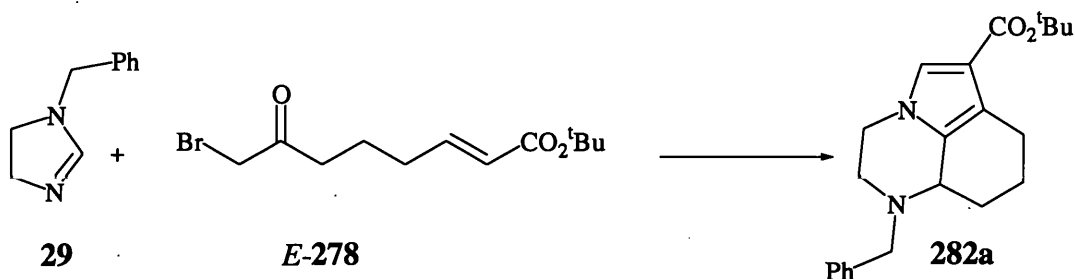
***tert*-Butyl *E*-8-bromo-7-oxooct-2-enoate**



Prepared as for methyl *E*-8-bromo-7-oxooct-2-enoate **196a**, but using *tert*-butyl *E*-7-oxooct-2-enoate (4 g; 18.8 mmol), LDA (22.6 mmol), chlorotrimethylsilane (11.93 ml; 94 mmol), triethylamine (13.10 ml; 94 mmol), NaHCO_3 (2.21 g; 26.3 mmol) and *N*-bromo succinimide (4.35 g; 24.4 mmol). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (7 : 93 v/v) as eluant to afford the *title compound* as a brown oil (2.20 g; 40%): ν_{\max} (film) / cm^{-1} 2978, 1713, 1654, 1477, 1393, 1368, 1318, 1295, 1155, 982, 890; δ_{H} (300MHz) 1.48 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.79 (quin, 2H, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.21 (m, 2H,

$\text{CH}_2\text{CH}=\text{CH}$), 2.68 (t, 2H, $J = 7.3$, COCH_2CH_2), 3.71 (BrCH_2CO), 5.76 (dt, 1H, $J = 1.6$, 15.5, $\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 6.80 (dt, 1H, $J = 6.7$, 15.5, $\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$); δ_{C} (75MHz) 22.0 ($\text{CH}_2\text{CH}_2\text{CH}_2$), 28.1 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 30.9 ($\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 34.1 (BrCH_2CO), 38.7 (COCH_2CH_2), 80.3 ($\text{CH}=\text{CHCO}_2\text{C}(\text{CH}_3)_3$), 123.9 ($\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 146.2 ($\text{CH}_2\text{CH}=\text{CHCO}_2^t\text{Bu}$), 165.8 (CO_2^tBu), 201.4 (CH_2COCH_2); m/z (CI) 308 (MNH_4^+ , 7%), 230 (49%), 175 (10%), 174 (100%), 158 (13%), 52 (21%); (EI) 137 (6%), 95 (7%), 81 (8%), 68 (19%), 57 (100%), 41 (67%); (Found: (CI): MNH_4^+ 308.0856; $\text{C}_{12}\text{H}_{19}\text{BrO}_3$ requires MNH_4^+ 308.0861).

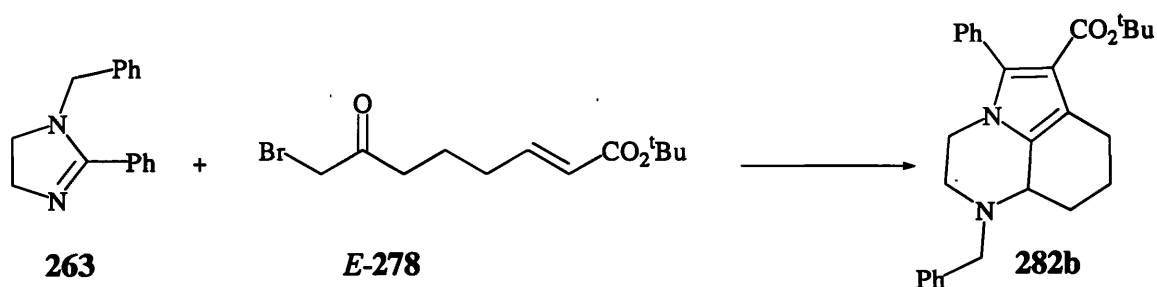
***tert*-Butyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate**



To a solution of 1-benzyl-4,5-dihydroimidazole (0.19 g; 1.21 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate (0.39 g; 1.34 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.22 ml; 1.45 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (15 : 85 v/v) as eluant to afford the *title compound* as a yellow oil (0.14 g; 33%): ν_{max} (film) / cm^{-1} 2983, 1736, 1698, 1524, 1466, 1374, 1246, 1174, 1096, 1048, 914, 735; δ_{H} (300MHz) 1.47

(dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.52 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.74 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.08 (m, 1H, 8-CHH), 2.27 (m, 1H, 9-CHH), 2.47 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 2-CHH), 2.63 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.85 (dd, 1H, $J = 6.4, 16.8$, 7-CHH), 3.00 (ddd, 1H, $J = 2.3, 3.9, 12.5$, 2-CHH), 3.12 (d, 1H, $J = 13.2$, PhCH_2), 3.27 (br. d, 1H, $J = 10.6$, 9a-CH), 3.82 (m, 2H, 3- CH_2), 4.22 (d, 1H, $J = 13.2$, PhCH_2), 7.07 (s, 1H, 5-CH), 7.28-7.32 (m, 5H, Ar-H); δ_{C} (75MHz) 22.0, 22.6 (C-8 and C-7), 27.8 (C-9), 28.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 44.9 (C-2), 49.7 (C-3), 57.1 (PhCH_2), 59.6 (C-9a), 79.1 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 115.7 (C-6a), 116.6 (C-6), 124.1 (C-5), 128.1, 128.3, 128.9 ($3 \times \text{Ar-CH}$), 130.5 (C-9b), 138.5 (Ar-C), 165.0 ($\text{CO}_2\text{C}(\text{CH}_3)_3$); m/z (EI) 353 (MH^+ , 28%), 324 (21%), 268 (38%), 177 (32%), 91 (100%), 65 (15%), 57 (50%), 41 (33%); (Found: (EI): MH^+ 353.2228; $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$ requires MH^+ 353.2229).

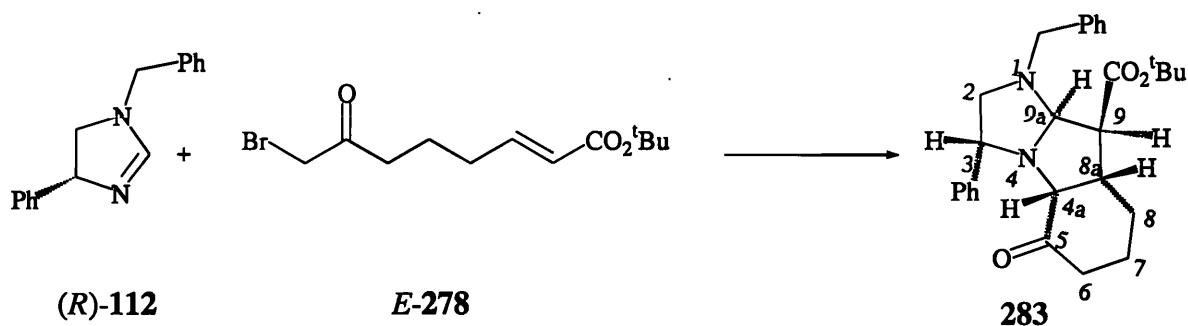
***tert*-Butyl 6-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate**



To a solution of 1-benzyl-2-phenyl-4,5-dihydroimidazole (0.22 g; 0.94 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate (0.30 g; 1.03 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.17 ml; 1.12 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The reaction was cooled, the solvent was removed

under reduced pressure residue purified by silica gel column chromatography using ethyl acetate / hexane (7.5 : 92.5 v/v) as eluant to afford the *title* compound as a white solid (0.14 g; 34%): m.p. 52-54°C; ν_{\max} (nujol) / cm^{-1} 2927, 2855, 1687, 1460, 1377, 1164, 1148; δ_{H} (300MHz) 1.27 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.51 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-CHH), 1.81 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-CHH), 2.15 (m, 1H, 8-CHH), 2.30 (m, 1H, 9-CHH), 2.42 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 2-CHH), 2.74 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-CHH), 2.93 (m, 2H, 7-CHH and 2-CHH), 3.09 (d, 1H, $J = 13.4$, PhCH_2), 3.32 (br. d, 1H, $J = 10.6$, 9a-CH), 3.46 (ddd, 1H, $J = 7.5, 10.0, 12.5$, 3-CHH), 3.57 (ddd, 1H, $J = 2.3, 3.9, 12.5$, 3-CHH), 4.23 (d, 1H, $J = 13.4$, PhCH_2), 7.26-7.30 (m, 10H, Ar-H); δ_{C} (75MHz) 22.5, 22.8 (C-8 and C-7), 27.9 (C-9), 28.1 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 44.0 (C-2), 49.9 (C-3), 57.1 (PhCH_2), 59.6 (C-9a), 78.7 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 112.9 (C-6a), 117.3 (C-6), 126.9, 127.6, 127.7, 128.2, 128.3, 128.8 ($6 \times \text{Ar-CH}$), 130.4 (C-9b), 132.4 (C-5), 136.8, 138.4 ($2 \times \text{Ar-C}$), 164.5 ($\text{CO}_2\text{C}(\text{CH}_3)_3$); m/z (EI) 429 (MH^+ , 12%), 401 (21%), 400 (77%), 371 (9%), 355 (7%), 345 (13%), 344 (100%), 253 (8%), 91 (100%), 65 (8%), 57 (43%); (Found: C, 77.70; H, 7.48; N, 6.32%; (EI): MH^+ 429.2546; $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 0.25 \text{ MeOH}$ requires C, 77.72; H, 7.62; N, 6.42%; MH^+ 429.2542).

***tert*-Butyl (3*R*,4*aR*,8*aS*,9*S*,9*aR*)-1-benzyl-5-oxo-3-phenyldecahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate**



To a solution of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole (0.26 g; 1.12 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate (0.36 g; 1.23 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.20 ml; 1.35 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The reaction was cooled, the solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) as eluant to afford the *title compound* as a white solid (0.15 g; 31%). Recrystallisation from methanol / hexane gave white needles for X-ray crystallographic analysis: m.p. 169-171°C; $[\alpha]_D^{20} = +14.25$; $c = 2$; DCM); ν_{\max} (nujol) / cm^{-1} 2926, 2855, 1715, 1490, 1379, 1219, 1147; δ_{H} (300MHz) 1.45 (s, 9H, $\text{CO}_2\text{C}(\text{CH}_3)_3$), 1.80-1.82 (m, 2H, 8-*CHH* and 7-*CHH*), 1.90-1.92 (m, 2H, 8-*CHH* and 7-*CHH*), 2.14 (m, 1H, 6-*CHH*), 2.32 (dd, 1H, $J = 9.2, 10.0$, 2-*CHH*), 2.50 (m, 1H, 6-*CHH*), 2.83 (t, 1H, $J = 6.9$, 9-*CH*), 3.17 (m, 1H, 8*a*-*CH*), 3.22 (d, 1H, $J = 12.9$, CH_2Ph), 3.25 (dd, 1H, $J = 5.5, 9.2$, 2-*CHH*), 3.62 (d, 1H, $J = 6.6$, 4*a*-*CH*), 4.09 (dd, 1H, $J = 5.5, 10.0$, 3-*CH*), 4.11 (d, 1H, $J = 12.9$, CH_2Ph), 4.58 (d, 1H, $J = 6.9$, 9*a*-*CH*), 7.28-7.32 (m, 10H, Ar-*H*); δ_{C} (75MHz) 24.2 (*C*-8), 26.2 (*C*-7), 28.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 39.3 (*C*-6), 45.5 (*C*-8*a*), 53.5 (*C*-9), 58.6 (CH_2Ph), 63.0 (*C*-2), 68.1 (*C*-3), 73.0 (*C*-4*a*), 81.2 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 86.7 (*C*-9*a*), 126.6, 126.9, 127.2, 128.1, 128.2, 128.9 (6 \times Ar-*CH*), 138.1 and 141.2 (2 \times Ar-*C*), 170.3 ($\text{CO}_2\text{C}(\text{CH}_3)_3$), 210.3

(C-5); m/z (EI) 447 (MH^+ , 28%), 389 (90%), 373 (63%), 369 (22%), 345 (38%), 299 (61%), 291 (100%), 250 (46%), 249 (52%), 91 (100%), 57 (70%), 43 (16%), 41 (33%);
(Found: (EI): MH^+ 447.2646; $C_{28}H_{34}N_2O_2$ requires MH^+ 447.2647).

References

References

1. W. Scheithauser, G. V. Komek and A. Marzell, *Brit. J. Cancer*, 1998, **77**, 1349.
2. A. R. Katritzky and C. W. Rees, in *Comprehensive Heterocyclic Chemistry*; C. W. Bird and G. W. H Cheeseman, Ed.; Pergamon Press, 1984, Vol. 5, Part 4A.
3. G. Desimoni, G. Taconni, A. Bario, G. P. Pollini, in *Natural Product Synthesis Through Pericyclic Reactions*, ACS monograph 180, American Chemical Society: Washington, DC, 1984, Chapt. 5.
4. For a review in cycloadditions see: C. P. Dell, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3873.
5. (a) A. Padwa, in *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; John Wiley & Sons: New York, 1984, Vol.1, Chapter 1; (b) K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, 1996, **50**, 652; (c) G. Broggini and G. Zecchi, *Gazz. Chim. Ital.*, 1996, **126**, 479; (d) E. J. Kantorowski and M. J. Kurth, *Mol. Diversity*, 1996, **2**, 207; (e) M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
6. A. R. Mattocks, in *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: New York, 1986.
7. R. J. Molineux, in *Alkaloids: Chemical and Biological Perspective*; S. W. Pelletier, Ed.; John Wiley & Sons: New York, 1987, Vol. 5, Chapt. 1.
8. R. Huisgen, *Proc. Chem. Soc.*, 1961, 357.
9. G. Bianchi, C. De Micheli and R. Gandolfi, in *The Chemistry of Double-Bonded Functional Groups*; S. Patai, Ed.; John Wiley & Sons: London, 1977, Vol. 1, Part 1, p 369.
10. K. N. Houk and K. Yamaguchi, in *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; John Wiley & Sons: New York, 1984, Vol.2, p 407.

11. W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990, p 269.
12. T. Curtius, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2230.
13. R. Huisgen, *Angew. Chem.*, 1963, **75**, 604.
14. R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; John Wiley & Sons: New York, 1984, Vol.1, p 1.
15. R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403.
16. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633.
17. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 321; For a review see: P. N. Confalone, E. M. Huie, *Org. React.*, 1988, **36**, 1.
18. (a) R. A. Firestone, *J. Org. Chem.*, 1968, **33**, 2285; (b) R. A. Firestone, *J. Chem. Soc.*, 1970, 1570; (c) R. A. Firestone, *J. Org. Chem.*, 1976, **41**, 403; (d) R. A. Firestone, *Tetrahedron*, 1977, **33**, 3009.
19. K. N. Houk, R. A. Firestone, L. Munchausen, P. H. Mueller, B. H. Arison and L. A. Garcia, *J. Am. Chem. Soc.*, 1986, **108**, 6401.
20. K. N. Houk, *Acc. Chem. Res.*, 1975, **8**, 36.
21. A. Komornicki, J. D. Goddard and H. F. Schaefer III, *J. Am. Chem. Soc.*, 1980, **102**, 1763.
22. I. Fleming, in *Frontier Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976.
23. a) R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
b) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 781.
24. K. Fukui, *Tetrahedron Lett.*, 1965, 2009.

25. The relative energies of the relevant FMO's can be calculated using the second order perturbation theory energy equation. For more detailed information see: G. Klopman, *J. Am. Chem. Soc.*, 1968, **90**, 223.
26. L. Salem, *J. Am. Chem. Soc.*, 1968, **90**, p 543.
27. M. J. S. Dewar, R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum Press, New York, 1975.
28. R. Sustman, *Pure App. Chem.*, 1974, **40**, 569.
29. R. Sustman, *Tetrahedron Lett.*, 1971, 2717.
30. R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291.
31. (a) R. Grigg and J. Kemp, *J. Chem. Soc., Chem. Commun.*, 1978, 109; (b) R. Grigg and J. Kemp, *Tetrahedron Lett.*, 1980, **21**, 1461.
32. D. A. Barr, M. J. Dorrity, R. Grigg, J. F. Malone, J. Montgomery, S. Rajviroongit and P. Stevenson, *Tetrahedron Lett.*, 1990, **31**, 6569.
33. R. Grigg, J. Montgomery and A. Somasunderam, *Tetrahedron*, 1992, **48**, 10431.
34. S. Kanemasa and H. Yamamoto, *Tetrahedron Lett.*, 1990, **31**, 3633.
35. (a) R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi and T. Pilati, *Tetrahedron: Asymmetry*, 1991, **2**, 1329; (b) S. G. Pyne, J. Safaci and F. Koller, *Tetrahedron Lett.*, 1995, **36**, 254.
36. Y. D. Gong, S. Nadji, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 3081.
37. E. Vedejs and R. Martinez, *J. Am. Chem. Soc.*, 1979, **102**, 7993.
38. R. Smith and T. Livinghouse, *Tetrahedron*, 1985, **41**, 3559.
39. R. Grigg, P. Kennewell, V. Savia and V. Sridharan, *Tetrahedron*, 1992, **48**, 10423.
40. (a) O. Tsuge, S. Kanemasa and K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997; (b) O. Tsuge, S. Kanemasa, M. Ohe and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4079.
41. R. C. F. Jones, J. R. Nichols and M. T. Cox, *Tetrahedron Lett.*, 1990, **31**, 2333.

42. R. C. F. Jones, K. J. Howard, J. R. Nichols and J. S. Snaith, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2061.
43. (a) L. M. Harwood, A. S. Anslow, H. Phillips, D. Watkin and L. F. Wong, *Tetrahedron: Asymmetry*, 1991, **2**, 169; (b) L. M. Harwood, A. S. Anslow, H. Phillips, D. Watkin and L. F. Wong, *Tetrahedron: Asymmetry*, 1991, **2**, 1343.
44. R. M. Williams, in *Synthesis of Optically Active α -Amino Acids*; Pergamon Press, 1989, 114.
45. V. Caplar, A. Lisini, F. Kajfez, D. Kalbah and V. Sunjic, *J. Org. Chem.*, 1978, **43**, 1355.
46. A. Padwa, Y. Chen, U. Chiacchio and W. Dent, *Tetrahedron*, 1985, **4**, 3529.
47. P. Deprez, J. Royer and H. Husson, *Tetrahedron*, 1991, **2**, 1189.
48. R. M. Williams, W. Zhai, D. J. Aldous and S. C. Aldous, *J. Org. Chem.*, 1992, **57**, 6527.
49. G. Galley, J. Liebscher and M. Patzel, *J. Org. Chem.*, 1995, **60**, 5005.
50. Z. Ma, S. Wang and C. Cooper, *Tetrahedron: Asymmetry*, 1997, **8**, 883.
51. G. A. Cordell, in *Introduction to Alkaloids-A Biogenetic approach*; John Wiley & Sons, 1981, Chapter 3.
52. C. Wittland, U. Florke and N. Risch, *Synthesis*, 1997, 1291.
53. F. Laduron, C. Ates and H. G. Viehe, *Tetrahedron Lett.*, 1996, **37**, 5515.
54. F. Felluga, P. Nitti, G. Pitacco and E. Valentin, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2331.
55. E. Vedejs, S. Larsen and F. G. West, *J. Org. Chem.*, 1985, **50**, 2170.
56. A. Viso, R. F. Pradilk, C. G. Strachan, M. Alonso, M. Ripoll and I. Andre, *J. Org. Chem.*, 1997, **62**, 2316.
57. C. Ibarra, A. Csaky, I. Silanes and M. Quiroga, *J. Org. Chem.*, 1997, **62**, 479.

58. W. J. Evans, T. S. Gammersheimer and J. W. Ziller, *J. Am. Chem. Soc.*, 1995, **117**, 8999.
59. (a) N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Org. Chem.*, 1988, **53**, 4570; (b) A. R. Carrol, B. F. Bowden and J. C. Coll, *Aust. J. Chem.*, 1993, **46**, 489; (c) A. Heim, A. Terpin and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 155; (d) F. Ishibashi, Y. Miyazaki and M. Iwao, *Tetrahedron*, 1997, **53**, 5951.
60. M. Banwell, B. Flynn and D. Hockless, *J. Chem. Soc., Chem. Commun.*, 1997, 2259 and references therein.
61. K. H. Park, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 113.
62. (a) C. A. Lopes and G. G. Trigo, *Adv. Heterocycl. Chemistry*, 1985, **38**, 177; (b) N. Kakajima, K. Itoi and Y. Takamatsu, *Antibiotics*, 1991, **44**, 293.
63. P. Deprez, J. Rouden, A. Chiaroni, C. Richie, J. Royer and H. P. Husson, *Tetrahedron Lett.*, 1991, **32**, 7531.
64. J. Rouden, J. Royer and H. P. Husson, *Tetrahedron Lett.*, 1989, **30**, 5133.
65. R. Grigg, *Tetrahedron: Asymmetry*, 1995, **6**, 2475.
66. D. M. Cooper, R. Grigg, S. Hargreaves, P. Kennewell and J. Redpath, *Tetrahedron*, 1995, **51**, 7791.
67. D. A. Barr, M. J. Dorrity, R. Grigg, S. Hargreaves and J. Malone, *Tetrahedron*, 1995, **51**, 273.
68. T. Coulter, R. Grigg, J. F. Malone and V. Shridharan, *Tetrahedron Lett.*, 1991, **32**, 5417.
69. R. Grigg, V. Shridharan, S. Suganthan and A. W. Bridge, *Tetrahedron*, 1995, **51**, 295.
70. R. Grigg, Z. Rankovic, M. Thornton-Pett and A. Somasunderam, *Tetrahedron*, 1993, **49**, 8679.
71. D. A. Barr, G. Donegan and R. Grigg, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1550.

72. D. A. Barr, G. Donegan, R. Grigg, H. Q. N. Gunaratne, J. Kemp, P. McMeekin and V. Sridharan, *Tetrahedron*, 1988, **44**, 557.
73. E. Keller, B. De Lange, M. T. Rispens and B. L. Feringa, *Tetrahedron*, 1993, **49**, 8899.
74. A. H. Fray and A. I. Meyers, *Bull. Chim. Soc. Fr.*, 1997, **134**, 283.
75. A. H. Fray and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 3362.
76. M. E. Kopach, A. H. Fray and A. I. Meyers, *J. Am. Chem. Soc.*, 1996, **118**, 9876.
77. A. H. Fray and A. I. Meyers, *Tetrahedron Lett.*, 1992, **33**, 3575.
78. P. Allway and R. Grigg, *Tetrahedron Lett.*, 1991, **32**, 5817.
79. R. Grigg, M. I. Lansdell and M. Thornton-Pett, *Tetrahedron*, 1999, **55**, 2025.
80. R. C. F. Jones and K. J. Howard, *J. Chem. Soc., Perkin Trans., 1*, 1993, 2391.
81. O. Tsuge, S. Kanemasa and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3137.
82. H. Ardill, M. J. R. Dorrity, R. Grigg, M. S. Leon-Ling, M. F. Malone, V. Sridharan and S. Thianpatanagul, *Tetrahedron*, 1990, **46**, 6433.
83. H. Ardill, X. L. R. Fontaine, R. Grigg, D. Henderson, J. Montgomery, V. Shridharan and S. Surendrakumar, *Tetrahedron*, 1990, **46**, 6449.
84. R. C. F. Jones, I. Turner and K. J. Howard, *Tetrahedron Lett.*, 1993, **34**, 6329.
85. R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Lett.*, 1996, **37**, 1707.
86. R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Lett.*, 1996, **37**, 1711.
87. R. C. F. Jones and J. R. Nichols, *Tetrahedron Lett.*, 1767.
88. A. F. McKay, *J. Org. Chem.*, 1951, **16**, pp. 1395, 1402.
89. H. Kohn, M. J. Cravey, J. H. Arceneaux, R. L. Cravey and M. R. Willcolt, III, *J. Org. Chem.*, 1977, **42**, 941.
90. H. Meerwein, in *Organic Synthesis*, Collect. Vol. V, Wiley & Sons, New York, 1973, pp. 1080 and 1096.
91. K. A. Hackl and H. Falk, *Monatsh. Chem.*, 1992, **123**, 599.

92. For a review on thionation reactions employing Lawesson's Reagent see: M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.
93. P. J. Stang, G. Maas, D. L. Smith and J. A. McCloskey, *J. Am. Chem. Soc.*, 1981, **103**, 4837.
94. H. Yukawa, T. Nagatami, Y. Torisawa, Y. Okaichi, N. Tada, T. Furuta, J. Minamikawa and T. Nishi, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1267.
95. J. M. Hook, *Synth. Commun.*, 1985, **14**, 83.
96. T. R. Kelly, T. E. Schmidt and J. Haggerty, *Synth. Commun.*, 1972, 544.
97. R. C. F. Jones, K. J. Howard and J. S. Snaith, *Tetrahedron Lett.*, 1997, **38**, 1647.
98. M. Murakami, Y. Okita, H. Matsuda, T. Okino and K. Yamaguchi, *Tetrahedron Lett.*, 1994, **35**, 3129.
99. M. Murakami, K. Ishida, T. Okino, Y. Okita, H. Matsuda and K. Yamaguchi, *Tetrahedron Lett.*, 1995, **36**, 2785.
100. K. Ishida, Y. Okita, H. Matsuda, T. Okino and M. Murakami, *Tetrahedron*, 1999, **55**, 10971.
101. B. M. Trost, K. Hiroi and L. N. Jungheim, *J. Org. Chem.*, 1980, **45**, 1839.
102. Y. Hon, L. Lu and S. Li, *J. Chem. Soc., Chem. Commun.*, 1990, 1627.
103. R. D. Little, D. P. Fox, L. Van Hijfte, R. Dannecker, G. Sowell, R. L. Wolin, L. Moens and M. M. Baizer, *J. Org. Chem.*, 1988, **53**, 2287.
104. F. Dumas and J. D'Angelo, *Tetrahedron: Asymmetry*, 1990, **1**, 167.
105. R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929.
106. M-J. Villa and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1569.
107. B. C. Ranu and S. Bhar, *Tetrahedron*, **48**, 1327.

108. For a review on ketone/aldehyde protection see: F. A. J. Meskens, *Synthesis*, 1980, 501.
109. I. Smonou, S. Khan, C. S. Foote, Y. Elenes, I. M. Mauridis, A. Pantidou and M. Orfanopoulos, *J. Am. Chem. Soc.*, 1995, **117**, 7081.
110. Cf. ^1H and ^{13}C data for similar systems: (a) R. C. F. Jones, P. Dimopoulos, S. C. Coles, M. E. Light and M. B. Hursthouse, *J. Chem. Soc. Perkin Trans. 1*, 2000, 2331; (b) M. W. Anderson, M. J. Begley and R. C. F. Jones, *J. Chem. Soc. Perkin Trans. 1*, 1984, 2599.
111. (a) P. Couture and J. Warkentin, *Can. J. Chem.*, 1997, **75**, 1281; (b) S. Kobayashi, M. Isube and T. Saegusa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1921.
112. G. Bartoli, M. Bosco, M. C. Belluci, E. Marcantoni, L. Sambri and E. Torregiani, *Eur. J. Org. Chem.*, 1999, 617.
113. The Open University CHEM777 Residential School: Organic Chemistry project and S344 Organic Chemistry booklet 1.
114. Prepared from (2-benzylamino)ethylamine and ethyl benzimidate hydrochloride: K. J. Howard, Ph.D. Thesis, University of Nottingham, 1995.
115. (a) R. K. Bansal, C. B. Jain and N. Gupta, *J. Ind. Chem. Soc.*, 1994, **71**, 203; (b) R. K. Bansal, C. B. Jain, N. Gupta, V. Kabra, K. Karaghiosoff and A. Schmidpeter, in *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **86**, 139.
116. See, for example: (a) A. Richardson, *J. Org. Chem.*, 1965, **30**, 2589; H. Suschitzky, B. J. Wakefield and R. A. Whittaker, *J. Chem. Soc., Perkin Trans. 1*, 1975, 401; (b) A. N. Grinev, Y. I. Trofinkin, E. V. Lumanova, N. I. Adreeva and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 1978, **12**, 80; (c) Bagatskii *et al.*, *Khim. Geterotskl. Soedin.*, 1979, **15**, 839; (d) A. N. Grinev and E. V. Lomanova, *Khim. Geterotskl. Soedin.*, 1983, **19**, 1690; (e) Y. Sudoh, K. Onitsuka, K. Imafuku and H. Matsumura, *Bull. Chem. Soc.*

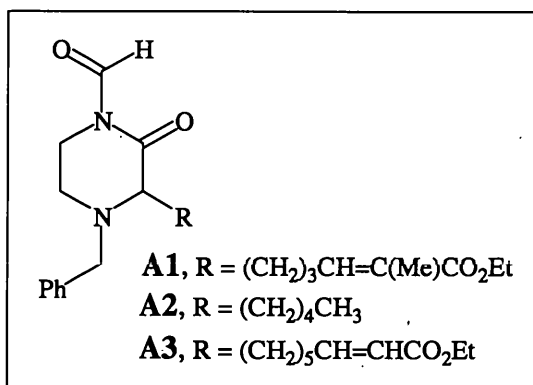
- Jpn.*, 1983, **56**, 3358; (f) A. Walser, T. Flynn, C. Manson, H. Crowley, C. Mareska, B. Jaremko and M. O'Donnell, *J. Med. Chem.*, 1991, **34**, 1209; (g) M. Kubicki, T. W. Kindoop, M. V. Caparelli and P. W. Coddling, *Can. J. Chem.*, 1994, **72**, 2028; (h) R. Nagata, N. Tanno, T. Kodo, N. Ae, H. Yamaguchi, T. Nishimura, F. Antoku, T. Tatsuno, T. Kato, Y. Tanaka and M. Nakamura, *J. Med. Chem.*, 1994, **37**, 3956; (i) J. W. Mickelson, E. J. Jacobsen, D. B. Carter, H. K. Im, W. B. Im, P. J. K. D. Schreuer, V. H. Sethy, A. H. Tang, J. E. McGee and J. D. Peake, *J. Med. Chem.*, 1996, **39**, 4954.
117. US Patent no. 3813392, *Chem. Abs.*, 1974, **81**, 49700; US Patent no. 3891643, *Chem. Abs.*, 1975, **83**, 147502; US Patent no. 3892746, *Chem. Abs.*, 1975, **83**, 147503; US Patent no. 4087527, *Chem. Abs.*, 1978, **89**, 109587; US Patent no. 4075206, *Chem. Abs.*, 1978, **88**, 190901.
118. D. E. Goldberg and K. C. Patel, *J. Inorg. Nucl. Chem.*, 1972, **34**, 3583.
119. H. Baganz, *Chem. Ber.*, 1965, **98**, 2170.
120. L. I. Kruse, C. Kaiser, W. E. De Wolf, J. A. Finkelstein and S. James, *J. Med. Chem.*, 1990, **33**, 781.
121. T. Lob, *Recl. Trav. Chim. Pays-Bas*, 1936, 859, 866.
122. F. Martell, *J. Am. Chem. Soc.*, 1950, **72**, 1032.
123. O. Isler, H. Gutmann, M. Montaron, R. Ruegg, G. Ryser and P. Zeller, *Helv. Chim. Acta*, 1957, **40**, 1242.
124. I. Matsuda, S. Sato, *J. Organomet. Chem.*, 1986, 47.
125. M. Larchveque, G. Valette and T. Cuvigny, *Synth., Commun.*, 1977, 424.
126. G. B. Subramaniam and S. Ahuja, *Ind. J. Chem. Soc., sect B*, 1966, **35**, 1043.
127. A. Mondon, *Angew. Chem.*, 1952, **11**, 224.
128. B. M. Trost, K. Hiroi and L. N. Jungheim, *J. Org. Chem.*, 1980, **45**, 1839.

129. S. S. Novikov and G. A. Shvekhgeimer, *Izv. Akad. Nauk. SSR, Ser. Khim.*, 1960, 2061.
130. B. V. Kovalev, *J. Org. Chem. (USSR)*, 1969, **5**, 437.
131. D. S. Hays, G. C. Fu, *Tetrahedron*, 1999, **55**, 8815.
132. M. P. Cooke and D. L. Burman, *J. Org. Chem.*, 1982, **42**, 4959.

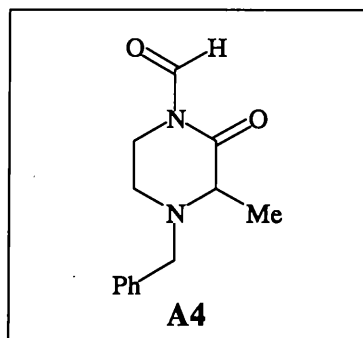
Addendum

Addendum

The reaction of α -bromomethylketones **224**, **239** and **253** with 1-benzyl-4,5-dihydroimidazole **29** gives rise to products of structures **A1-A3**.

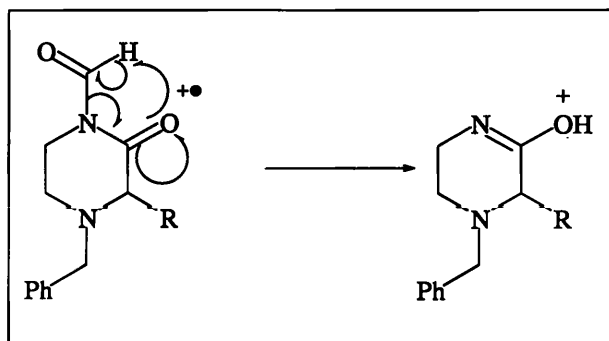


Moreover, reaction of chloroacetone **A5** under analogous conditions gives rise to compound **A4**.



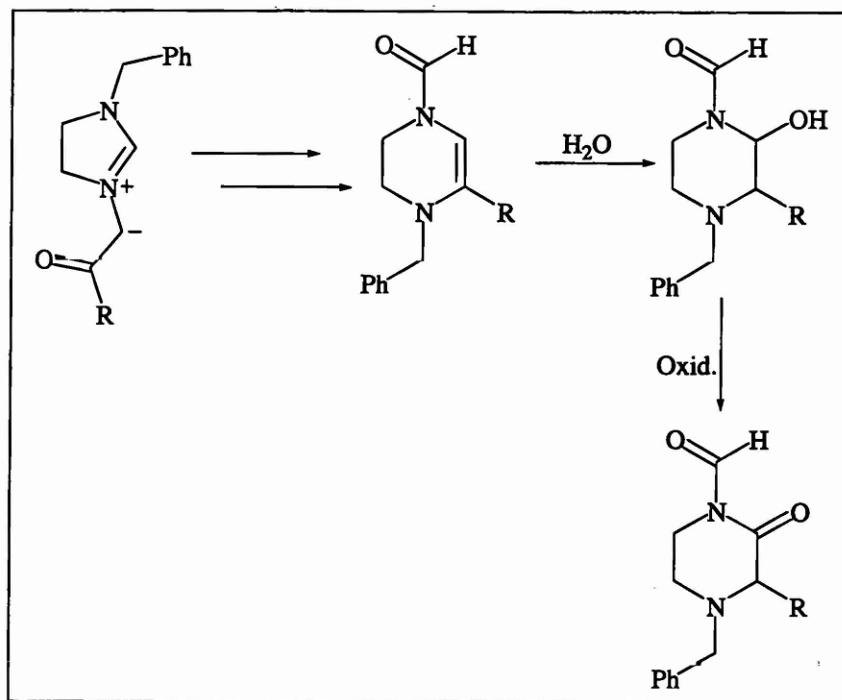
This structure is entirely consistent with the spectroscopical data, for example, in compounds **A2** and **A4** (which lack the conjugated ester functionality) the infra-red spectra exhibit two carbonyl stretches at 1695 and 1725 cm^{-1} that are the symmetric and asymmetric vibrations characteristic of an N-formylimide involving a six-membered ring lactam.^{a1-a3} Furthermore, the ^1H NMR signal of the formyl proton in such structures is

found in the region δ 9.2-9.5, as observed for our compounds. In the ^{13}C NMR spectra the signals at δ 162 and δ 173 can be attributed to the formyl and lactam carbonyl carbons. Finally, the mass spectra exhibited molecular ions consistent with the above formulation and also an M-28 fragment that can be accounted for the by the loss of CO as shown in Scheme A1.



Scheme A1

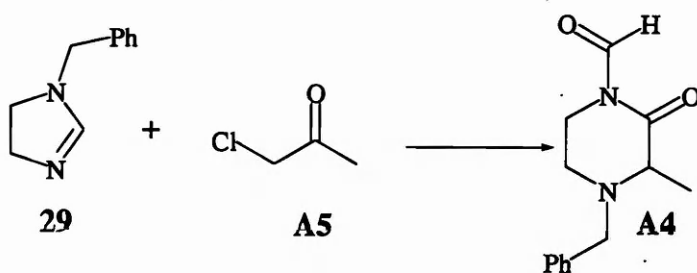
The formation of compounds **A1-A4** probably follows a similar pathway as the formation of compound **232** involving hydrolytic ring-opening of the 1,3-dipole followed by recyclisation to form the piperazine ring (Scheme A2). However, the formation of **A1-A4** formally requires the rehydration and oxidation of the tetrahydropiperazine ring. It is unclear why these latter two reactions should take place.



Scheme A2

Additional Experimental

4-benzyl-1-formyl-3-methyl-piperazine-2-one



Prepared as for 1-benzyl-4-formyl-2-(4-nitrophenyl)-1,4,5,6-tetrahydropyrazine **232** but using 1-benzyl-4,5-dihydroimidazole **29** (0.66 g; 4.12 mmol) and commercial chloroacetone (0.40 ml; 4.95 mmol). After purification of the residue by silica gel column chromatography using ethyl acetate / hexane (1 : 9 v/v) the *title* compound was isolated as

a orange oil (0.45 g; 47%): ν_{\max} (film) / cm^{-1} 1725, 1695, 1455, 1470, 1250; δ_{H} (300 MHz) 1.52 (d, 3H, $J = 4.8$ Hz, PhNCHCH_3), 2.5 (m, 1H, 5- CH_2), 3.0 (m, 1H, 5- CH_2), 3.35 (q, 1H, $J = 4.8$ Hz, 3- CH), 3.38 (d, 1H, $J = 10.6$ Hz, CH_2Ph), 3.42 (m, 1H, 6- CH_2), 3.67 (m, 1H, 6- CH_2), 3.94 (d, 1H, $J = 10.6$ Hz, PhCH_2), 7.28-7.32 (m, 5H, Ar- H), 9.44 (s, 1H, NCHO); δ_{C} (75 MHz) 15.3 (PhNCHCH_3), 40.7 (C-5), 44.9 (CH_2Ph), 57.9 (C-6), 61.1 (C-3), 127.6, 128.4, 128.7 ($3 \times \text{Ar-CH}$), 137.1 (Ar-C), 162.6 (NCHO), 173.7 (NCOCHN); m/z (CI) 233 (MH^+ , 100%), 205 ($\text{MH}^+ - \text{CO}$, 100%); (Found: (CI) MH^+ 232.1292; $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$ requires M^{*+} 232.1290)

Additional References

- a1. J. C. Gramain and R. Remuson, *Synth., Commun.*, 1982, 264.
- a2. N. Murugesan and M. Shamma, *Tetrahedron. Lett.*, 1979, **47**, 4521.
- a3. J-C. Gramain, R. Remuson and Y. Troin, *Tetrahedron*, 1979, **35**, 759.

Appendix

Table 1. Crystal data and structure refinement for **264a**.

Empirical formula	$C_{25}H_{26}N_2O_2$	
Formula weight	386.48	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P-1$	
Unit cell dimensions	$a = 11.448(2)$ Å	$\alpha = 86.50(3)^\circ$
	$b = 11.905(2)$ Å	$\beta = 87.96(3)^\circ$
	$c = 15.067(3)$ Å	$\gamma = 77.45(3)^\circ$
Volume	$2000.1(7)$ Å ³	
Z	4	
Density (calculated)	1.283 Mg / m ³	
Absorption coefficient	0.082 mm ⁻¹	
$F(000)$	824	
Crystal	Block; colourless	
Crystal size	$0.14 \times 0.12 \times 0.12$ mm ³	
θ range for data collection	$3.08 - 27.48^\circ$	
Index ranges	$-12 \leq h \leq 13, -15 \leq k \leq 15, -18 \leq l \leq 18$	
Reflections collected	17728	
Independent reflections	7744 [$R_{int} = 0.1722$]	
Completeness to $\theta = 27.48^\circ$	84.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9903 and 0.9887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7744 / 0 / 526	
Goodness-of-fit on F^2	0.867	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0682, wR2 = 0.1036$	
R indices (all data)	$R1 = 0.2781, wR2 = 0.1613$	
Extinction coefficient	$0.0014(3)$	
Largest diff. peak and hole	0.237 and -0.237 e Å ⁻³	

Diffractionmeter: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill Ewald sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, *Acta Cryst. A* 51 (1995) 33–37; R. H. Blessing, *J. Appl. Cryst.* 30 (1997) 421–426). **SHELXS97** (G. M. Sheldrick, *Acta Cryst.* (1990) A46 467–473). **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Table 2. Crystal data and structure refinement for **264b**.

Empirical formula	$\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2$	
Formula weight	386.48	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 10.559(2)$ Å	$\alpha = 90^\circ$
	$b = 9.6567(19)$ Å	$\beta = 112.47(3)^\circ$
	$c = 11.052(2)$ Å	$\gamma = 90^\circ$
Volume	$1041.5(4)$ Å ³	
Z	2	
Density (calculated)	1.232 Mg / m ³	
Absorption coefficient	0.078 mm ⁻¹	
$F(000)$	412	
Crystal	Block; colourless	
Crystal size	$0.25 \times 0.25 \times 0.10$ mm ³	
θ range for data collection	$1.99 - 27.48^\circ$	
Index ranges	$-13 \leq h \leq 13, -12 \leq k \leq 12, -13 \leq l \leq 14$	
Reflections collected	12212	
Independent reflections	4640 [$R_{\text{int}} = 0.0362$]	
Completeness to $\theta = 27.48^\circ$	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9922 and 0.9807	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4640 / 1 / 264	
Goodness-of-fit on F^2	1.043	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0373, wR2 = 0.0836$	
R indices (all data)	$R1 = 0.0507, wR2 = 0.0897$	
Absolute structure parameter	0.6(10)	
Extinction coefficient	0.031(3)	
Largest diff. peak and hole	0.172 and -0.147 e Å ⁻³	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill Ewald sphere). **Data collection and cell**

refinement: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*,

part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing,

Acta Cryst. A 51 (1995) 33–37; R. H. Blessing, *J. Appl. Cryst.* 30 (1997) 421–426).

Table 3. Crystal data and structure refinement for **277a**.

Empirical formula	$C_{20}H_{24}N_2O_2$	
Formula weight	324.41	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P-1$	
Unit cell dimensions	$a = 5.3447(11)$ Å	$\alpha = 81.91(3)^\circ$
	$b = 10.854(2)$ Å	$\beta = 87.82(3)^\circ$
	$c = 14.722(3)$ Å	$\gamma = 88.80(3)^\circ$
Volume	844.8(3) Å ³	
Z	2	
Density (calculated)	1.275 Mg / m ³	
Absorption coefficient	0.083 mm ⁻¹	
$F(000)$	348	
Crystal	Needle; colourless	
Crystal size	0.30 × 0.05 × 0.02 mm ³	
θ range for data collection	1.90 – 27.43°	
Index ranges	$-6 \leq h \leq 6, -14 \leq k \leq 14, -19 \leq l \leq 19$	
Reflections collected	12313	
Independent reflections	3729 [$R_{int} = 0.1814$]	
Completeness to $\theta = 27.43^\circ$	97.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9983 and 0.9756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3729 / 0 / 219	
Goodness-of-fit on F^2	0.944	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0566, wR2 = 0.1034$	
R indices (all data)	$R1 = 0.1507, wR2 = 0.1318$	
Extinction coefficient	0.017(4)	
Largest diff. peak and hole	0.239 and -0.261 e Å ⁻³	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell**

refinement: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*,

part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption**

correction: *SORTAV* (R. H. Blessing,

Acta Cryst. A 51 (1995) 33–37; R. H. Blessing, *J. Appl. Cryst.* 30 (1997) 421–426). **Program used to solve structure:**

SHELXS97 (G. M. Sheldrick, *Acta Cryst.* (1990) A46 467–473).

Table 4. Crystal data and structure refinement for **283**.

Empirical formula	$C_{28}H_{34}N_2O_3$	
Formula weight	446.57	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 5.8566(4)$ Å $b = 22.8548(18)$ Å $c = 9.1424(7)$ Å	$\beta = 92.913(6)^\circ$
Volume	$1222.14(16)$ Å ³	
Z	2	
Density (calculated)	1.214 Mg / m ³	
Absorption coefficient	0.079 mm ⁻¹	
$F(000)$	480	
Crystal	Colourless block	
Crystal size	$0.20 \times 0.20 \times 0.10$ mm ³	
θ range for data collection	$3.48 - 24.71^\circ$	
Index ranges	$-6 \leq h \leq 6, -26 \leq k \leq 24, -10 \leq l \leq 10$	
Reflections collected	6900	
Independent reflections	3346 [$R_{int} = 0.0585$]	
Completeness to $\theta = 24.71^\circ$	94.0 %	
Max. and min. transmission	0.9922 and 0.9845	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3346 / 1 / 299	
Goodness-of-fit on F^2	1.014	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0500, wR2 = 0.0957$	
R indices (all data)	$R1 = 0.0842, wR2 = 0.1075$	
Absolute structure parameter	Not reliably determined	
Extinction coefficient	$0.028(3)$	
Largest diff. peak and hole	0.181 and -0.178 e Å ⁻³	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, *Acta Cryst. A* 51 (1995) 33–37; R. H. Blessing, *J. Appl. Cryst.* 30 (1997) 421–426). **Program used to solve structure:** *SHELXS97* (G. M. Sheldrick, *Acta Cryst.* (1990) A46 467–473). **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. Relative chirality C1 = S, C6 = R, C13 = R, C15 = R, C16 = S